Volume 2 of 3

Tick Repellents: Past, Present, and Future

Data Requirements

OPPTS 810.3700: Insect Repellents for Human Skin and Outdoor Premises

Authors
Brooke W. Bissinger
R. Michael Roe

Study Completed on
June 24, 2009

Study Submitter
HOMS L.L.C.
PO Box 724
Clayton, NC 27520

Performing Laboratory
Department of Entomology
North Carolina State University
Raleigh, NC 27695-7613

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No information in this volume is claimed confidential on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: HOMS L.L.C

Company Agent: Heather R Bjor — January 6, 2010

Heather Bjornson
Regulatory Assistant

Date

GOOD LABORATORY PRACTICES STATEMENT

The submitter of this study was neither the sponsor of this study nor conducted it, and does not know whether it has been conducted in accordance with 40 CFR Part 160.

Company: HOMS L.L.C

Company Agent: Heather Bjor January 6, 2010

Heather Bjornson
Regulatory Assistant

Date

Pesticide Biochemistry and Physiology xxx (2009) xxx–xxx

Contents lists available at ScienceDirect

Pesticide Biochemistry and Physiology

journal homepage: www.elsevier.com/locate/pest

Review

Tick repellents: Past, present, and future

Brooke W. Bissinger, R. Michael Roe *

Department of Entomology, North Carolina State University, Campus Box 7647, Raleigh, NC 27695-7613, USA

ARTICLE INFO

Article history:
Received 24 June 2009
Accepted 25 September 2009
Available online xxxx

Keywords:
Repellent
Natural repellent
Tick
BioUD
Deet
IR3535
Oil of lemon eucalyptus
Permethrin
Picaridin

ABSTRACT

Ticks are important vectors of human and animal diseases. One important protective measure against ticks is the use of personal arthropod repellents. Deet and the synthetic pyrethroid permethrin currently serve as the primary personal protective measures against ticks. Concern over the safety of deet and its low repellency against some tick species has led to a search for new user-approved, efficacious tick repellents. In this article, we review the history and efficacy of tick repellents, discovery of new repellents, and areas in need of attention such as assay methodology, repellent formulation, and the lack of information about the physiology of repellency.

1. Introduction

Ticks vector the widest array of disease-causing organisms of all hematophagous arthropods and are second only to mosquitoes in their capacity to transmit disease agents of importance to human and veterinary health [1]. Tick control and disease prevention are largely dependent on the use of chemical acaricides. However, a number of problems are associated with acaricide use such as environmental pollution, contamination of meat and milk from livestock, development of resistance, and expense, especially in the developing world [2,3]. For humans, the most effective means of preventing tick attachment and contraction of tick-vectored disease organisms is by limiting exposure to tick habitat, thorough self-examination after contact with tick habitat, and use of personal arthropod repellents [4].

Arthropod repellents are defined as chemical substances that cause an arthropod to make oriented movements away from its source [5]. Deet (*N,N*-diethyl-3-methylbenzamide) has been the most extensively used personal arthropod repellent for over five decades and is available in a wide range of concentrations and products that can be applied to exposed skin or clothing [6] (Table 1). Deet is a broad-spectrum repellent that is highly effective against several species of mosquitoes [7,8], other biting flies, and chiggers [6]. Deet is also effective against ticks [9,10] but is generally considered to be less repellent than permethrin or piperidines [9,11–13].

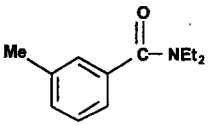
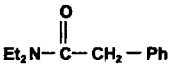
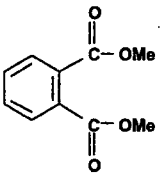
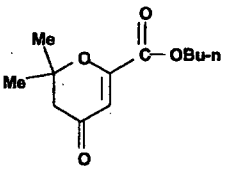
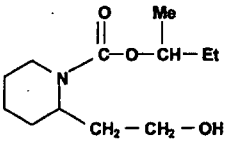
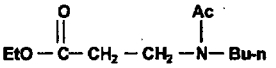
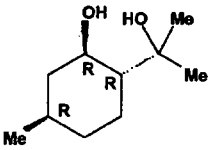
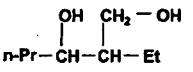
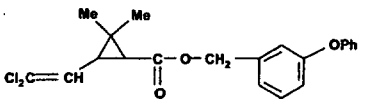
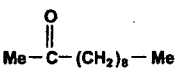
Deet is used annually by approximately 30% of the US population and 25% of the people in the United Kingdom [14]. The odor and skin-feel of deet is disagreeable to some people and deet reacts with some plastics and synthetic rubber. Adverse health effects attributed to the use of deet have been reported but the number of cases is relatively small compared to the number of people who use it [6]. Still, the safety of deet is doubted by some [15] promoting development of alternative repellents for the portion of the population that chooses not to use deet-based products. Presently two deet alternatives are recommended by the Centers for Disease Control and Prevention (CDC) that are labeled for use against ticks on human skin by the US Environmental Protection Agency (EPA): IR3535 (3-[*N*-butyl-*N*-acetyl]-aminopropionic acid, ethyl ester) and the piperidine, Picaridin (1-piperidine carboxylic acid) [16]. The synthetic pyrethroid permethrin is also approved for use on clothing for protection from ticks.

An ideal repellent should provide protection against a broad spectrum of blood-feeding arthropods for at least 8 h, be non-toxic, non-irritating, odorless, and non-greasy [17]. Such a repellent has yet to be developed. Typically, repellent-discovery has been driven by the need to protect military troops from hematophagous arthropods that vector human diseases [18]. Increased international travel and the movement of people from urban to rural areas now expose many civilians to arthropod-vectored pathogens [19,20] and have increased public interest in repellents. Repellent-discovery in part involves sophisticated computer-assisted, three-dimen-

* Corresponding author. Fax: +1 919 515 4325.
E-mail address: michael_roe@ncsu.edu (R.M. Roe).

0048-3575/$ - see front matter © 2009 Published by Elsevier Inc.
doi:10.1016/j.pestbp.2009.09.010

Table 1
Active ingredients commonly found in commercially available tick repellents.

Chemical name	IUPAC name	CAS number	Chemical formula	Structure
Deet, Diethyl toluamide	*N,N*-Diethyl-3-methyl-benzamide	134-62-3	$C_{12}H_{17}NO$	
DEPA, *N,N*-diethyl-2-phenyl-ethanamide	*N,N*-Diethyl-2-phenyl-acetamide	2431-96-1	$C_{12}H_{17}NO$	
DMP, dimethyl phthalate	Dimethyl benzene-1,2-dicarboxylate	131-11-3	$C_{10}H_{10}O_4$	
Dodecanoic acid, lauric acid	Dodecanoic acid	8045-27-0	$C_{12}H_{24}O_2$	
Indalone	Butyl 6,6-dimethyl-4-oxo-5H-pyran-2-carboxylate	8039-36-9	$C_{12}H_{18}O_4$	
Icaridin, KBR 3023, Picaridin	1-Piperidine carboxylic acid	119515-38-7	$C_{12}H_{23}NO_3$	
IR3535, EBAAP	3-[*N*-butyl-*N*-acetyl]-aminopropionic acid ethyl ester	52304-36-6	$C_{11}H_{21}NO_3$	
PMD, *para*-menthane-3,8-diol, Quwenling	(1R,2R,5R)-2-(2-Hydroxypropan-2-yl)-5-methyl-cyclohexan-1-ol	81176-88-7	$C_{10}H_{20}O_2$	
Ethyl hexanediol, Rutger's 612	2-Ethylhexane-1,3-diol	94-96-2	$C_8H_{18}O_2$	
Permethrin	(3-Phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropane-1-carboxylate	52645-53-1	$C_{21}H_{20}Cl_2O_3$	
2-Undecanone, methyl nonyl ketone	Undecan-2-one	112-12-9	$C_{11}H_{22}O$	

Please cite this article in press as: B.W. Bissinger, R.M. Roe, Tick repellents: Past, present, and future, Pestic. Biochem. Physiol. (2009), doi:10.1016/j.pestbp.2009.09.010

sional molecular modeling [19] as well as the traditional evaluation of biologically-based compounds [21–26]. While the use of repellents for personal protection against mosquitoes has been reviewed before [17,27], less attention has been given to tick repellents. In this review, we examine the past, present, and future discovery and use of repellents for personal protection from ticks.

2. Sensory perception

Ticks locate their host by two mechanisms: ambushing and hunting (or a combination of the two strategies as in the lone star tick, *Amblyomma americanum* (L.)). For the former and more common strategy, ticks climb foliage where they wait for a passing vertebrate host with their forelegs extended anterolaterally. This behavior, known as questing, facilitates location of the host. Questing ticks will cling to a passing animal if direct contact is made [2]. Hunting ticks, on the other hand, respond to host stimuli by emerging from their refuges and rapidly searching out the host by walking toward the source of the stimuli [1]. Stimuli which induce ambush and hunting behavior include carbon dioxide, butyric and lactic acid, ammonia (from animal wastes), heat, shadows, and vibrations [1]. Ticks unlike mosquitoes lack antennae. Instead, they detect host cues using sensilla located on the tarsi of the front legs [28].

Until recently, relatively little research has been conducted to determine how ticks detect repellents. Carroll et al. [10] note that most repellency assays for ticks do not discriminate between repellency due to olfaction versus that from tactile chemoreception. Olfactory sensilla are able to detect vaporized molecules [29], and evidence suggests that olfaction is involved at least in part in repellency. For example, in a Y-tube bioassay, Dautel et al. [30] showed that nymphal sheep ticks, *Ixodes ricinus* (L.), that approached a deet-treated filter paper surface would come within 1–3 mm of the surface but not contact it. Additionally, the authors showed in a moving-object bioassay (discussed in more detail later) that deet was repellent to *I. ricinus* nymphs at a short (mm) distance. McMahon et al. [31] found that the repellent indalone presented in an air stream caused adult tropical bont ticks, *Amblyomma variegatum* F., to walk in the opposite direction of the source. Carroll et al. [10] in their bioassay wrapped repellent-treated fingers in organdy cloth to prevent direct physical contact with the repellent. Nymphal *A. americanum*, and blacklegged ticks, *Ixodes scapularis* Say (formerly *I. dammini*), were repelled in this assay by both deet and the repellent SS220 ((1*R*,2*S*)-2-methylpiperidinyl-3-cyclohexen-1-carboxamide) showing that repellency was obtained by olfaction alone. Tactile chemoreception also appears to play a role in repellency. In a moving-object bioassay, IPSS (10% w/v imidacloprid + 50% w/v permethrin spot-on solution), was determined to be a contact but not spatial repellent against adult paralysis ticks, *Ixodes holocyclus* Neumann [32]. The relative importance of olfaction versus tactile chemoreception in repellency is currently under appreciated. Until more research is conducted in this area, it will be difficult to understand the importance of these two mechanisms in the research and development of new repellents in the future.

Three major groups of proteins are involved in insect olfaction: odorant receptors, odorant-binding proteins, and odorant-degrading enzymes [33]. Numerous studies have shown that susceptibility to a repellent varies between tick species [9,23,34] and life stages [11,13,35], but the molecular basis for these differences is unknown. The physiology of repellency in ticks is poorly understood. The mode of action of deet in mosquitoes has been debated for some time. Previously, it was thought that deet inhibited mosquito attraction to lactic acid [36]. More recently, Ditzen et al. [37] found that deet inhibited responses to 1-octen-3-ol. This view was contested by Syed and Leal [38] who showed that mosquitoes exhibited no difference in response to 1-octen-3-ol alone or in combination with deet. Syed and Leal [38] also showed that deet was repellent to mosquitoes even in the absence of host cues, and odorant receptor neurons were able to respond to deet stimulation directly. Our understanding of the mode of action of tick repellents is in its infancy especially as compared to insects. A better understanding of the molecular mechanisms of repellent chemoreception including the role of the central nervous system would be valuable in advancing our basic understanding of the sensory physiology of the acarines and the rational design of next generation repellents.

3. Assay methods for tick repellency

One problem in the research and development of new tick repellents is the lack of a standardized testing method. Early discovery of repellents sought to rapidly identify broad-spectrum, non-irritating, non-plasticizing repellents that exhibited long-lasting efficacy, and little thought was given to developing a standardized testing method [40]. Even today, a wide range of methods is employed when testing tick repellents. Studies differ in the timeframe in which repellency is examined, the species and life stages used, the formulation and amount of active ingredient tested, applications of repellent to different types of materials that may or may not affect repellent volatilization, the use of an animal host or not, the utilization of different types of tick behaviors in the bioassay, variability in the consideration of tactile versus spatial repellency, and laboratory versus field assay approaches. These variations in testing methodology and assay conditions make comparison among studies problematic and difficult to relate to the day-to-day real world use of repellents for personal protection. In a 2004 review, Dautel [40] grouped the methods available for testing putative tick repellents into three broad categories: (1) those that are performed in the absence of hosts or host stimuli, (2) performed in the presence of host stimuli, and (3) performed using a live host.

Tests conducted in the absence of a host are easy to standardize and can be conducted rapidly and at a low cost. For example, Witting-Bissinger et al. [26] and Bissinger et al. [34] conducted a simple choice test between a treated and untreated surface in Petri dishes. Repellency in this case was determined by the number of ticks found on the treated versus untreated surface and compared in separate experiments with ticks in an arena with no repellent. Climbing bioassays can be used with ticks that exhibit ambushing behavior. These tests use vertical rods [41–43] or strips of fabric [44] treated at some level above the base of the vertical climb with a repellent barrier. Ticks that climb past the barrier are considered not repelled while those that retreat or fall from the treated surface are repelled. Unlike Petri dish bioassays, climbing bioassays confirm that ticks are indeed host-seeking based on their questing behavior at the time of the assay. Field tests also can be conducted in the absence of a host by comparing the number of questing ticks collected on treated and untreated cloths dragged over the ground in tick-infested habitat [24,45–47]. The laboratory tests mentioned here do not place human subjects at risk; however, it is important to note that in cloth drag tests, the human dragging the cloth is at risk of exposure to tick bites. For all of these assays, i.e., the Petri dish, climbing, and cloth drag tests, the procedure is easy to perform, rapid, and inexpensive. However, an overestimate of repellency in the absence of host cues is possible [40].

Tests that incorporate a tick attractant, especially that mimic as close as possible or involve an actual host, should more accurately represent the practical use of a repellent. Moving-object bioassays and olfactometers where the test compound is presented at a distance from the tick can be used to exclusively evaluate spatial repellency. The moving-object bioassay [30] uses a heated rotating drum to mimic body heat and movement of the host. Compounds

are applied to a raised surface on the drum and questing ticks are positioned so they can contact the raised portion as it passes. For olfactometers, ticks can be provided a choice between the host odorant alone versus host odorant with repellent or a choice between air with and without repellent. In this case, the odorants and repellents merge from each arm of the Y-tube presenting the tick a choice. Disadvantages of both the rotating drum and Y-tube olfactometer tests are the need for specialized equipment, and for the former, only one test run can be conducted at a time [40].

The ideal measure of repellency is a field trial in tick-infested habitat comparing human volunteers who apply a repellent to their clothing or skin to those who remain untreated. This type of study tests the repellent against wild populations of ticks rather than laboratory-reared specimens and under the conditions that would be found during practical usage. However, such tests are difficult to conduct because of the number of human volunteers needed for sufficient replication and time needed to conduct the assay. Animals may be substituted for human hosts under field [48] or laboratory conditions [12,35,49,50] and can be used to directly measure reduction of tick attachment. However, the animals used may not be the preferred host of the tick, resulting in an incorrect estimation of repellency [40]. Tests using live hosts also place animals and humans at risk to disease transmission and require approval by an Institutional Animal Care and Use Committee (IACUC) or an Institutional Review Board (IRB), respectively. Laboratory bioassays using a live host can reduce the chance of disease transmission if the ticks used are obtained from a disease-free colony. Laboratory studies are also useful because they allow control of environmental conditions. Both field and laboratory studies using humans place subjects at risk of allergic reactions from tick bites. Additionally, the chemicals used in repellency studies may have weakly established toxicity profiles.

One compromise to the field test that incorporates host cues is the fingertip assay, a modified laboratory climbing bioassay [9,10,23,51,52]. The index finger of a human subject is treated with a band of repellent proximal to the distal end of the digit leaving the finger tip untreated. The finger is positioned vertically with the fingertip touching the center of an arena containing ticks. Those that crawl above the treated zone of the finger are not repelled while those that retreat or fall off the treated surface are repelled. Similar tests have been conducted to simulate natural habitats in the laboratory where the arena may contain grass [53] or dry leaf litter, i.e., the simulated forest floor method [54]. The repellent is applied to the socks or in a band around the ankles of the subject who stands in the container and the number of ticks that cross the treated area is recorded as not repelled.

What is greatly needed are comparative studies of the various methods for repellency testing, especially studies between practical field tests involving human volunteers or animal subjects versus potential laboratory tests without a host that might mimic the field test. One such study by Matthewson et al. [55] found a poor correlation of results for different compounds in the presence and absence of a host for the red-legged tick, *Rhipicephalus evertsi evertsi* (Neumann). Apparently xenobiotic metabolism, different binding properties (to clothing, hair and skin), and *trans*-epithelial transport can potentially affect the activity of a repellent [55]. For this reason, additional research is needed to develop a model laboratory test without the need for a host that can accurately mimic the day-to-day use of repellents for personal protection or to control ticks on animals.

4. The first synthetic repellents

Prior to World War I and the emergence of synthetic chemical repellents, arthropod repellents were primarily plant-based [56] with oil of citronella being the most widely used compound and standard against which others were tested [39]. Three synthetic repellents existed before World War II: dimethyl phthalate (DMP) which was discovered in 1929, indalone (butyl-3,3-dihydro-2,2-dimethyl-4-oxo-2H-pyran-6-carboxylate) which was patented in 1937, and ethyl hexanediol (also known as Rutgers 612) which was made available in 1939 (Table 1). These three compounds were later combined into a formulation for military use termed 6-2-2 or M-250 (six parts DMP, and 2 parts each indalone and Rutgers 612) [39]. Synthetic repellents were developed principally to protect military troops from arthropod-borne disease and were heavily researched by the US military during World War II. From 1942 to 1949, the United States Department of Agriculture (USDA) tested more than 7000 compounds for repellent properties. During WWII, thousands of compounds were tested for repellency against biting arthropods including mosquitoes and chiggers [18,57]; however, little attention was paid to tick repellents [58]. In the mid to late 1940s and early 1950s a number of studies were conducted examining various compounds applied to clothing for use against ticks. Some compounds including *n*-butylacetanilide, *n*-propylacetanilide, undecylenic acid, and hexyl mandelate were highly effective against ticks but were never commercialized and made available for civilian use [39]. Here the early synthetic repellents that were available commercially are discussed with the inclusion of 6-2-2 which was available for military use.

4.1. DMP

Dimethyl phthalate was originally developed as a solvent [59]. It exhibits low toxicity with no adverse effects observed in rabbits exposed daily to dermal applications of 1000 mg/kg and a mouse LD_{50} of 6900 mg/kg [59]. DMP is a broad-spectrum repellent that was used widely from the 1940s to the 1980s before being replaced by other active ingredients. It was commonly used in China before being replaced by Quwenling (*para*-menthane-3,8-diol, PMD) and was the standard repellent in India before DEPA (*N,N*-diethyl-2-phenyl-acetamide) [59].

Results from studies examining the repellency of DMP were mixed. Adult *A. americanum* were not repelled by DMP applied to uniforms, and although DMP was initially effective in preventing attachment of nymphal *A. americanum*, repellency fell below 50% by the third day of testing [53]. In contrast, Brennan [58] found that DMP applied to socks worn by human volunteers provided complete protection for 4 weeks against adult *A. americanum* but gave little protection against the Rocky Mountain wood tick, *Dermacentor andersoni* Stiles. DMP reduced the number of ticks attached to humans by half compared to controls when uniforms were treated once in a 5 d period and 5× fewer ticks were attached when uniforms were treated twice in a 6 d period [53]. Hadani et al. [49] examined repellent effects of DMP against larval and nymphal *Hyalomma excavatum* Koch on their gerbil host *Meriones tristrami* Thomas. DMP (applied at 50 mL/animal) provided 50% repellency against larvae and nymphs at concentrations of 0.4% and 2.6%, respectively. At the same application rate, 90% repellency against larvae was observed at a concentration of 1.1% and 7.6% for nymphs. In this study, DMP was less repellent against both life stages than the pesticide benzyl benzoate and two isomers of deet. DMP was also repellent against all life stages of the fowl tick, *Argas persicus* (Oken), and brown dog ticks, *Rhipicephalus sanguineus* (Latreille), but less repellent than deet or DEPA [35].

4.2. Indalone

In general, indalone was considered more effective for the prevention of tick bites than other early synthetic repellents, including deet [59]; however, in some studies, indalone was ineffective [45,60]. The oral toxicity of indalone is low (mouse LD_{50}

13,700 mg/kg), but kidney and liver damage was observed in rodents exposed to indalone for an extended period of time [59]. Indalone has also been noted as having an unpleasant smell [53].

Military uniforms treated with indalone provided over 70% protection from adult and nymphal *A. americanum* 2 weeks after treatment [53]. Similarly, indalone provided complete protection from nymphal and adult *A. americanum* and adult *I. scapularis* for 3 weeks after application to socks [53]. Fabric impregnated with an acetone solution of indalone provided ⩾90% repellency against *A. americanum* over 5 d of field-testing, and uniforms impregnated with the same solution provided >90% repellency for 30 d [61].

In contrast, Granett and French [45] found that coveralls and cloth drags treated with indalone provided only 49% and 76% repellency, respectively, 4 d after treatment compared to untreated materials. Additionally, indalone-treated coveralls that were washed twice and tested 7 weeks after treatment provided only 39% repellency against the American dog tick, *Dermacentor variabilis* Say [60]. An aerosol formulation of indalone applied to uniforms was also ineffective, providing only 22% repellency against ticks in field trials. However, an emulsion formulation provided 83% repellency from 4 to 6 weeks after treatment [62]. In a recent study, indalone presented in an air stream on a locomotion compensator decreased attraction of adult *A. variegatum* to their aggregation-attraction pheromone [31].

4.3. Ethyl hexanediol

Ethyl hexanediol (EH) like DMP was also developed originally as a solvent [59]. Strickman [59] suggested EH may be less useful as a repellent against ticks than with other arthropods. Few studies have examined the repellency of EH against ticks. Smith and Gouck [53] treated socks with EH and observed complete protection from *A. americanum* nymphs and *I. scapularis* adults 1 and 3 weeks after treatment; however, repellency against nymphal *A. americanum* declined to approximately 50% the fourth week after treatment. Products containing EH were eventually removed from US and Canadian markets in 1991 after toxicity was observed in laboratory animals [18].

4.4. 6-2-2

Different repellents were mixed to produce 6-2-2 (DMP: indalone: Rutgers 612) in an attempt to combine more than one mode of action, extend repellent duration, and broaden the range of efficacy [59]. Smith and Gouck [53] performed field trials examining repellency of uniforms treated with 6-2-2. The number of ticks attached to human volunteers was 3.2× less for uniforms treated once in a 5 d period with 6-2-2 than for controls. Uniforms treated twice with 6-2-2 over a 6 d period provided a 6.4× lower tick attachment compared to controls. In a third trial, uniforms treated with 6-2-2 applied from a sprayer reduced tick attachment 2.6–3.7× compared to controls over 5 d [53]. In a laboratory test under simulated natural conditions, 6-2-2 applied to socks worn by human volunteers provided 99–100% protection over 4 weeks of testing against *A. americanum* but provided insufficient repellency against *D. andersoni* [58].

5. Modern synthetic repellents

5.1. Deet

Use of the early synthetic repellents was overshadowed by the discovery of DEET which gradually became the gold standard for arthropod repellents [59]. Over 20,000 compounds have been screened for repellency against arthropods, yet none have resulted in a product of equal commercial success to that of deet with its broad-spectrum range of protection and duration of repellency [19]. Deet was formulated as an arthropod repellent in 1946 [63] and registered for commercial use in 1957. Deet is the active ingredient in the majority of commercially available tick repellents used on human skin today and is effective against several tick species. For example, deet was 90–100% repellent against a number of larval and adult *Haemaphysalis* spp. on filter paper treated 24 h before bioassays [64]. Deet also provided 98% repellency from 10 to 20 min after application against nymphal *A. americanum* and *I. scapularis* at 1.6 μmol/cm^2 in fingertip bioassays [10]. With this same assay approach, deet (0.3 mg/cm^2) provided 2.7 h protection against nymphal *A. americanum* but provided <1 h protection against *I. scapularis* nymphs [9]. A slow-release polymer formulation of 33% deet provided 97.65% repellency for 12 h against nymphal *A. americanum* in a simulated forest floor experiment using human volunteers [54].

Against some tick species, deet was unable to provide long-lasting protection even at relatively high concentrations. Jensenius et al. [65] tested the efficacy of four commercially available lotion formulations of deet against nymphal bont ticks, *Amblyomma hebraeum* Koch. Three deet products containing 19.5%, 31.6%, and 80% deet repelled ⩾90% of *A. hebraeum* 1 h after application, but 4 h after application provided <50% repellency. Similarly, Pretorius et al. [66] compared 20% lotion formulations of Picaridin and deet against nymphal *A. hebraeum* and found that overall deet outperformed Picaridin but only provided effective protection for 2 h. In field trials, a 33.25% extended-duration lotion formulation of deet applied to military battle dress uniforms provided 87.5% repellency against *I. scapularis* larvae but only provided 19.1% repellency against nymphs of the same species [11]. In the same study, deet was only 50% repellent to adult *D. variabilis* and nymphal and adult *A. americanum* and provided 61.4% repellency to larval *A. americanum* compared to controls. Deet was not repellent to adult *A. variegatum* in a study examining repellency in the presence of an attractant (an aggregation-attachment pheromone) even when presented at 10^6 times the amount of the attractant [31].

5.2. Permethrin

Permethrin is a synthetic pyrethroid insecticide that was registered in the US in 1979 and has been widely used for several decades against ticks and other arthropods (Table 1). Permethrin provides protection from several species of ticks; however, this protection is due primarily to its toxicity rather than repellency [67]. Permethrin can be applied to clothing and bed nets but should not be applied to skin [1].

Permethrin provided better protection than deet in a number of bioassays. For example, 0.5% permethrin applied to clothing provided 100% protection against nymphal and adult *A. americanum* [68] and *D. variabilis*, while a 20% spray of deet provided 85% and 94% protection against the same ticks, respectively [69]. Clothing treated with 0.5% permethrin also provided 100% protection of all life stages of *I. scapularis* while 20% and 30% deet provided 86% and 92% repellency, respectively, against the three life stages pooled together [70]. On baby mice treated to the point of repellent runoff, permethrin provided 95% effective control at a concentration of 0.14% while deet provided the same repellency at a concentration of 17.47% against nymphal *Ornithodoros parkeri* Cooley [50]. Buescher et al. [71] also found that permethrin was significantly more potent than deet against *O. parkeri*. In a field study, the number of Western blacklegged ticks, *Ixodes pacificus* Cooley and Kohls, collected from overalls treated with a 0.5% pressurized spray of permethrin did not differ significantly from that of untreated over-

alls [72]. However, ticks collected from treated overalls exhibited 100% morbidity/mortality 1 h after contact with treated overalls with fewer than 50% of the ticks recovering after 24 h. Similarly, significantly fewer active live ticks were collected from uniforms treated with permethrin (0.5% spray or 0.125% impregnant) than those treated with an extended-duration formulation of deet (33.25%) [11].

A new method of clothing impregnation using polymer-coating of permethrin onto fabric followed by heating to 130 °C increased the longevity of permethrin, which was still active after 100 launderings compared to standard dipping methods (US Army Individual Dynamic Absorption (IDA)-Kit and Peripel 10) [73]. Time to knockdown (inability of tick to move or migrate) of laundered treated fabric was measured for nymphal *I. ricinus*. Fabric treated by the factory polymer-coated method exhibited significantly greater knockdown than both the IDA-Kit and the Peripel 10 methods of fabric treatment. Complete knockdown of *I. ricinus* on factory polymer-coated fabric occurred after 7 min for unlaundered cloth and in 15.2 min after 100 launderings.

While toxicity of permethrin can be long-lasting, true repellency is short-lived. Lane and Anderson [67] compared repellency of permethrin-treated and untreated cotton surfaces and observed that initial repellency of permethrin wore off within 8–15 min for Pacific Coast ticks, *Dermacentor occidentalis* Marx, and within 4–8 min for pajaroello ticks, *Ornithodoros coriaceus* Koch. Some species of ticks appear to be less susceptible to permethrin than others. Fryauff et al. [74] exposed camel ticks, *Hyalomma dromedarii* (Koch), to fabric impregnated with permethrin and then placed ticks on rabbits and recorded the time to attachment. Interestingly, attachment was greater and more rapid in permethrin-exposed ticks than in controls. The authors hypothesized that permethrin induced a premature or excess release of a neurosecretory substance that stimulates attachment. The synthetic pyrethroid, cypermethrin, stimulated egg development in other tick species, *O. parkeri* and *O. moubata* (reviewed by [75]), suggesting that this class of chemistry may actually promote tick reproduction and feeding. Mortality in the former studies with *H. dromedarii* was low, and protection against permethrin may have been due to its thick chitin and cuticle that also offers protection from desiccation in the desert environment [76]. Resistance to permethrin and other pyrethroids has been observed in the southern cattle tick, *Rhipicephalus* (formerly *Boophilus*) [77] *microplus* (Canestrini) [78,79]. Resistance appears to be due to the presence of pyrethroid-hydrolyzing esterases [80–82] and a *trans*-permethrin hydrolyzing carboxylesterase [81]. Toxicity of permethrin can also vary with tick age. Eight-week old larval *A. hebraeum* and brown ear ticks, *Rhipicephalus appendiculatus* Neumann, were 8.8 and 1.5× more susceptible, respectively, to permethrin than 2-week old larvae [83].

5.3. DEPA

DEPA (*N,N*-diethyl-2-phenyl-acetamide) (Table 1) is a compound with moderate oral toxicity (mouse oral LD_{50} 900 mg/kg) [84] and low to moderate dermal toxicity (rabbit and female mouse LD_{50} of 3500 and 2200 mg/kg, respectively) [85,86] that was developed around the same time as deet. DEPA has recently regained interest and could prove to be an important repellent in developing countries because of its low cost, $25.40 per kg compared to $48.40 per kg for deet [18]. In India, DEPA is used as a repellent because of the lack of availability of 3-methylbenzoic acid, a compound necessary for the manufacture of deet [35].

Rabbits treated with 0.3 mL of 25% formulations of deet or DEPA were provided >90% repellency against larval *R. sanguineus* for 15 d after treatment. Deet provided >90% repellency against nymphal and adult *R. sanguineus* for 7 and 5 d, respectively, while DEPA provided the same repellency for 5 d against nymphs and 4 d against adults. Hens treated with 0.3 mL of 25% deet or DEPA were provided 11 and 7 d of >90% repellency, respectively, against larval *A. persicus*. Twenty-five percent treatments of deet or DEPA provided >90% repellency against *A. persicus* nymphs for 5 d and the same repellency against adult *A. persicus* for 4 d [35].

5.4. Piperidines

Some repellents have been developed based on piperidine, a colorless organic compound with a peppery odor. The structural motif is present in piperine, the alkaloid that gives pepper (*Piper* spp.) its hot flavor [27]. AI3-37220 (cyclohex-3-enyl 2-methylpiperidin-1-yl ketone) is a piperidine derivative whose insect repellent properties were first described by McGovern et al. in 1978 [87]. In field studies against adult and nymphal *A. americanum*, AI3-37220 provided significantly greater overall protection than deet [13]. Both repellents provided 100% repellency against nymphs immediately after application; however, 5 h later deet provided <60% repellency while AI3-37220 provided >90% repellency. Against adults, AI3-37220 provided >95% repellency immediately after application compared to approximately 85% repellency for deet. After 6 h, AI3-37220 provided approximately 80% repellency and deet <50% repellency. AI3-37220 also provided greater repellency than deet against *A. americanum* in vertical climbing bioassays but was slightly less repellent than deet against *I. scapularis* [88].

AI3-37220 is a racemic mixture with two asymmetrical centers. Achiral synthesis yields a mixture of four stereoisomers. The 1S, 2'S stereoisomer is the most effective against mosquitoes [89] and has been formulated into a compound called SS220 or Morpel 220. Rabbits treated with 20% Morpel 220 were completely protected from attachment by *A. americanum* for up to 72 h. Morpel 220 also significantly reduced attachment by adult *D. variabilis* compared to controls 72 h after application, although no difference in attachment was observed between Morpel 220-treated rabbits and controls at 0, 24, and 48 h [12]. SS220 provided 94% repellency against *A. americanum* and 100% repellency against *I. scapularis* in fingertip bioassays at concentrations of 0.8 μmol/cm^2 [10]. When applied at a rate of 155 nmol/cm^2, SS220 repelled 100% of *I. scapularis* nymphs and 84% of *A. americanum* nymphs in fingertip bioassays [23]. A 20% cream formulation of SS220 provided 100% repellency for 12 h against nymphal *A. americanum* in a simulated forest floor experiment [54]. In tests against nymphal *I. scapularis*, the effective concentration to repel 95% of the nymphs was 32.6 ± 3.9 nmol/cm^2 (the EC_{95} ± SE) for SS220 compared to 58.4 ± 62.4 nmol/cm^2 for deet [23].

Schreck et al. [9] tested a number of piperidine compounds against nymphal *A. americanum* and *I. scapularis*. A compound similar to AI3-37220, 1-(3-cyclohexenyl-carbonyl) piperidine (AI3-35765), provided the longest duration of protection against *A. americanum* (4 h, 1.5× longer than deet). Five other piperidine compounds provided between 2.3–3.0 h protection against *A. americanum*. However, none of the compounds tested provided >1 h protection time against *I. scapularis*.

Picaridin (1-piperidine carboxylic acid) (also known as Bayrepel®, KBR 3023, and Icaridin) is a colorless, nearly odorless piperidine analog that was developed by Bayer in the 1980s using molecular modeling [18,90] (Table 1). Picaridin became commercially available in the US in 2005 [91]. The compound exhibits low toxicity and is not a skin sensitizer [90]. In trials against nymphal *A. hebraeum*, 20% Picaridin provided effective repellency for 1 h; however, repellency declined to approximately 55% from 2 to 4 h after application [66]. In a simulated forest floor experiment, a 20% cream formulation of Picaridin provided 100% repellency against nymphal *A. americanum* for 12 h [54].

6. Plant-based repellents

Renewed interest in plant-based arthropod repellents was generated after the US EPA added a rule to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) in 1986 exempting compounds considered to be minimum risk pesticides [92]. Recently a large number of studies have emerged examining biologically-based repellents for use against ticks and other arthropods [21–26,34,52,97,98,101,128]. Increased interest in biologically-based repellents is also likely a response to the public perception that synthetic insect repellents such as deet are unsafe [15]. Additionally, registration of biologically-based repellents by the US EPA is generally more rapid than registration of synthetic compounds. Biopesticides (the term used by the EPA for naturally occurring substances that control pests) are often registered in less than 1 year while conventional pesticides are registered in an average of 3 years [93].

Plants produce numerous secondary compounds that serve as repellents, feeding deterrents, or toxicants to phytophagous insects [94]. Defensive phytochemicals are grouped into five broad categories: growth regulators, nitrogen compounds, phenolics, proteinase inhibitors, and terpenoids [27]. The vast majority of phytochemicals that have been tested for repellency against ticks are terpenoids. A number of plants and essential oils from plants also exhibit repellent properties against hematophagous arthropods including ticks (Tables 2 and 3).

6.1. Terpenoids

Terpenoids are a structurally diverse assembly of compounds that make up the largest group of secondary plant chemicals [95] and are involved in defense against herbivorous arthropods and pathogens [96]. Terpenes are derived from units of isoprene and are classified sequentially as chains of isoprene (hemi-, mono-, sesqui-, di-, etc.) [27]. Plant-derived terpenoids are repellent against several species of ticks. For example, Dautel et al. [30] found that *I. ricinus* nymphs spent significantly less time on filter paper treated with 1 mg/cm^2 of myrtenal, a bicyclic terpene that is a constituent of the essential oil of a number of plants including citronella, *Cymbopogon nardus* (L.) Rendle, peppermint, *Mentha* × *piperita* L., and lemon balm, *Melissa officinalis* L. [27] than on untreated controls. Tunón et al. [22] tested whole and fractioned compounds from the extract of southernwood, *Artemisia abrotanum* L., and the essential oil from the carnation flower, *Dianthus caryophyllum* L., against nymphal *I. ricinus*. Eight hours after treatment, the monocyclic terpene eugenol isolated from both plants provided >90% repellency while the acyclic terpene alcohol β-citronellol isolated from carnation flower oil provided 84.1% repellency. Similarly, oil of citronella, containing citronellol and geraniol repelled 83% of *I. ricinus* nymphs after 8 h and lily of the valley essential oil which also contains citronellol provided 67% repellency 8 h after application to filter paper [97]. Eugenol isolated from fractioned sweet basil, *Ocimum basilicum* (L.) provided equivalent repellency to deet against *I. ricinus* in Petri dish bioassays at 100 and 1000 μg doses but was less repellent at a 10 μg dose. In bioassays where treated or untreated filter paper were held in the palm of a human subject's hand, eugenol was repellent compared to controls but was less repellent than equivalent doses of deet [25]. Thorsell et al. [97] found that 10% clove oil, which contains high amounts of eugenol, provided 78% repellency while 10% deet provided 71% repellency against *I. ricinus* nymphs for 8 h.

Pålsson et al. [98] tested constituents in the essential oil from the flowers of aromatic tansy, *Tanacetum vulgare* L., against nymphal *I. ricinus*. Several terpenoid compounds (Table 3) and one blend of compounds provided greater percentage repellency than hexane controls with mean percentage repellencies ranging from 64.3% to 71.5%. Extracts and oils of wormwood, *Artemisia absinthium* L., sweetgale, *Myrica gale* L., and marsh tea, *Rhododendron tomentosum* (Stokes) were also tested against nymphal *I. ricinus* [46]. Monoterpenes isolated from *M. gale* were active; however, the extracts provided <50% repellency. A 10% dilution of *R. tomentosum* produced 95.1% repellency while an ethyl acetate extraction of *A. absinthium* provided 78.1% repellency. The primary volatile compounds identified in *A. absinthium* and *R. tomentosum* were the terpenes, myrtenyl acetate (77.8%) and (3Z)-hexanol (18.3%), respectively.

Table 2
Plants that exhibit repellency against ticks, their taxonomic families, tick species repelled, and references.

Scientific name	Common name	Family	Tick species	References
Andropogon gayanus	Gamba grass	Poaceae	*R. microplus*	[108,110]
Artemisia abrotanum	Southernwood	Asteraceae	*I. ricinus*	[22]
Azadirachta indica	Neem tree	Meliaceae	*I. ricinus*	[47]
Callicarpa americana	American beautyberry	Verbenaceae	*A. americanum, I. scapularis*	[23]
Callicarpa japonica	Japanese beautyberry	Verbenaceae	*A. americanum, I. scapularis*	[23]
Chamaecyparis nootkatensis	Alaska yellow cedar	Cupressaceae	*I. scapularis*	[99–101]
Cleome/Gynandropsis gynandra	African spider flower	Cappardaceae	*R. appendiculatus*	[43,114]
Cleome monophylla	Spider plant	Cappardaceae	*R. appendiculatus*	[42]
Commiphora erythraea	Sweet myrrh	Burseraceae	*A. americanum, D. variabilis, I. scapularis*	[44]
Commiphora holtziana	Gum haggar	Burseraceae	*R. microplus*	[116]
Commiphora swynnertonii		Burseraceae	*R. appendiculatus*	[117]
Convallaria majalis	Lily of the valley	Liliaceae	*I. ricinus*	[97]
Corymbia citriodora	Lemon-scented gum	Myrtaceae	*I. ricinus*	[46,124,125]
Cymbopogon spp.	Citronella grass	Graminae, Poaceae	*I. ricinus*	[97]
Dianthus caryophyllum	Carnation	Caryophyllaceae	*I. ricinus*	[22]
Humiria balsamifera	Oloroso	Humiriaceae	*A. americanum, I. scapularis*	[52]
Lavandula angustifolia	Lavender	Lamiaceae	*H. marginatum rufipes, I. ricinus*	[46,104]
Lycopersicon hirsutum f. glabratum	Wild tomato	Solanaceae	*A. americanum, D. variabilis, I. scapularis, O. parkeri*	[28,34,128]
Melinis minutiflora	Molasses grass	Poaceae	*R. appendiculatus*	[108,109]
Ocimum basilicum	Sweet basil	Lamiaceae	*I. ricinus*	[25]
Ocimum suave	Wild basil	Lamiaceae	*R. appendiculatus*	[41]
Pelargonium graveolens	Geranium	Geraniaceae	*I. ricinus*	[46]
Rhododendron tomentosum	Marsh tea	Ericaceae	*I. ricinus*	[21]
Stylosanthes hamata	Caribbean stylo	Fabaceae	*R. microplus*	[113]
Stylosanthes humilis	Townsville stylo	Fabaceae	*R. microplus*	[113]
Syzygium aromaticum	Clove	Myrtaceae	*I. ricinus*	[97]
Tanacetum vulgare	Tansy	Asteraceae	*I. ricinus*	[98]

[redacted]

Table 3
Tick repellent compounds isolated from various plants.

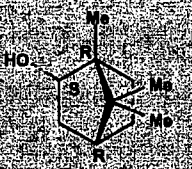
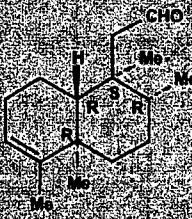
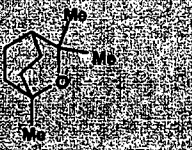
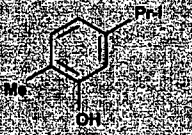
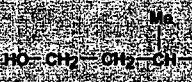
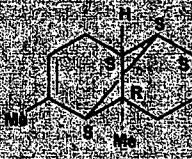
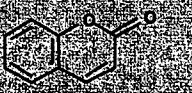
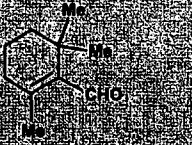
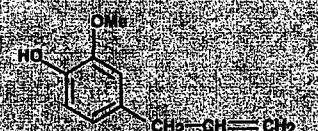
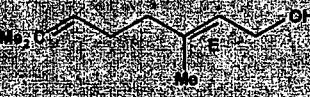
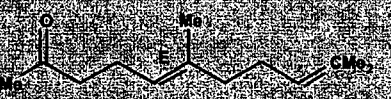
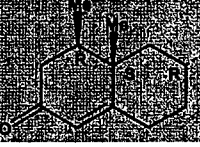
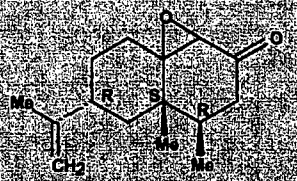
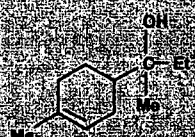
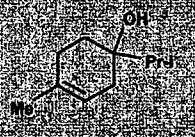
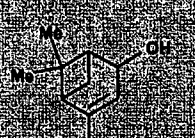
Compound name	Tick species repelled	Reference	Formula	Structure
Borneol	*I. ricinus*	[98]	$C_{10}H_{18}O$	
Calficarpenal	*A. americanum, I. scapularis*	[123]	$C_{16}H_{26}O$	
1,8-Cineol (eucalyptol)	*I. ricinus*	[98]	$C_{10}H_{18}O$	
Carvacrol	*I. scapularis, R. appendiculatus*	[42,43,101]	$C_{10}H_{14}O$	
β-Citronellol	*I. ricinus*	[22]	$C_{10}H_{20}O$	
α-Copaene	*R. appendiculatus*	[111]	$C_{15}H_{24}$	
Coumarin	*I. ricinus*	[22]	$C_9H_6O_2$	
β-Cyclocitral	*R. appendiculatus*	[43]	$C_{10}H_{16}O$	
m-Cymene	*R. appendiculatus*	[43]	$C_{10}H_{14}$	
Decanal	*Ixodes*	[134]	$C_{10}H_{20}O$	
Dodecanoic acid	*I. ricinus*	[12]	$C_{12}H_{24}O_2$	
2-Dodecanone	*R. appendiculatus*	[42]	$C_{12}H_{24}O$	

Table 3 (*continued*)

Compound name	Tick species repelled	Reference	Formula	Structure
Eugenol	*I. ricinus*	[22]	$C_{10}H_{12}O_2$	
trans-Geraniol	*R. appendiculatus*	[43]	$C_{10}H_{18}O$	
trans-Geranylacetone	*R. appendiculatus*	[43]	$C_{13}H_{22}O$	
(−)-Isolongifolenone	*A. americanum*, *I. scapularis*	[52]	$C_{15}H_{24}O$	
Humulene	*R. appendiculatus*	[42]	$C_{15}H_{24}$	
Methyl jasmonate	*I. ricinus*	[24]	$C_{13}H_{20}O_3$	
Myrenal	*I. ricinus*	[40]	$C_{10}H_{16}O$	
Nonanal	*R. appendiculatus*	[43]	$C_9H_{18}O$	
Verbol	*R. appendiculatus*	[43]	$C_{10}H_{18}O$	
α-Zingiberol	*R. appendiculatus*	[43]	$C_{15}H_{26}O$	
Nootkatone	*I. scapularis*	[101]	$C_{15}H_{22}O$	

(*continued on next page*)

Table 3 (*continued*)

Compound name	Tick species repelled	Reference	Formula	Structure
Nootkatone 1,10-epoxide	*I. scapularis*	[101]	$C_{15}H_{22}O_2$	
Octanal	*A. americanum, I. ricinus*	[139]	$C_8H_{16}O$	$OHC-(CH_2)_6-Me$
2-Phenylethanol	*I. ricinus*	[22]	$C_8H_{10}O$	$HO-CH_2-CH_2-Ph$
1-α-Terpineol	*I. ricinus, R. appendiculatus*	[42,43,98]	$C_{10}H_{18}O$	
4-Terpineol	*I. ricinus*	[98]	$C_{10}H_{18}O$	
Thujone	*I. ricinus*	[98]	$C_{10}H_{16}O$	
2-Undecanone	*A. americanum, D. variabilis, I. scapularis, O. parkeri*	[26,34,127]	$C_{11}H_{22}O$	$Me-C(=O)-(CH_2)_8-Me$
3-Undecanone	*R. appendiculatus*	[42]	$C_{11}H_{22}O$	$Et-C(=O)-(CH_2)_7-Me$
Valerenic-13-ol	*I. scapularis*	[101]	$C_{15}H_{26}O$	
Verbenol	*I. ricinus*	[98]	$C_{10}H_{16}O$	
1-Verbenone	*I. ricinus*	[98]	$C_{10}H_{14}O$	

Chemical structures were obtained from [139].

Two terpenoids, callicarpenal and intermedeol, isolated from American beautyberry, *Callicarpa americana* L. and Japanese beautyberry, *C. japonica* Thunb. have activity against ticks. Using a fingertip bioassay, Carroll et al. [23] compared deet and SS220 to callicarpenal and intermedeol against nymphal *A. americanum* and *I. scapularis*. Against *A. americanum*, only SS220 and intermedeol provided significant repellency compared to controls while all four compounds were highly repellent (≥96%) against *I. scapularis*. In dose–response tests, SS220 provided the greatest repellency against *I. scapularis*, however, no difference in repellency was found between callicarpenal, intermedeol, and deet. Callicarpenal applied to cloth provided 100% repellency against *I. scapularis* 3 h after application; however, repellency fell to 43.3% at 4 h [23].

Essential oil and fractioned compounds from the Alaska yellow cedar, *Chamaecyparis nootkatensis* (D. Don) Spach., possess acaricidal activity against *I. scapularis* nymphs [99,100]. Dietrich et al. [101] isolated 14 compounds classified as monoterpenes, eremophilane sesquiterpenes, and eremophilane sesquiterpene derivatives from the essential oil of the heartwood of Alaskan cedar. After an initial screening for tick repellency, the four most repellent compounds were compared to deet against nymphal *I. scapularis* in *in vitro* studies. No significant difference in the RC_{50} (concentration that produces 50% repellency) was found 4 h post-treatment between deet and the compounds carvacrol, nootkatone (derived from grapefruit oil but found in Alaskan cedar), nootkatone 1 → 10 epoxide, and valencene-13-ol.

Isolongifolenone is a sesquiterpene compound found in the South American tree, *Humiria balsamifera* St. (Aubl.) [52]. In fingertip bioassays, both isolongifolenone and deet applied at 78 nmol compound/cm^2 repelled 100% of *I. scapularis* nymphs. Isolongifolenone and deet were less repellent against *A. americanum* compared to *I. scapularis*, repelling only 80% of the nymphs at a concentration of 78 nmol compound/cm^2 [52].

6.2. Plant growth regulators

Methyl jasmonate is a volatile compound involved in the regulation of plant growth and development that is found in the essential oil of a number of plants [102]. Garboui et al. [24] tested different concentrations of methyl jasmonate on cotton cloth against nymphal *I. ricinus*. Methyl jasmonate at a concentration of 0.3 and 0.75 mg/cm^2 provided 92% and 99% repellency, respectively, compared to untreated controls. Field trials were also conducted to compare repellency between treated and untreated flannel cloth drags. Cloth treated with 0.2 mg/cm^2 methyl jasmonate exhibited 80.9% repellency on the first day of testing; however, repellency dropped to 28.5% on the second day with the same cloth that was tested.

Plant essential oils are generally less efficacious and provide an acceptable level of protection for less time after application than deet or permethrin because of their high volatility [27,103]. This problem can be overcome by the use of higher concentrations. Jaenson et al. [21] showed that 1% diluted oils from *R. tomentosum* did not provide significant repellency against nymphal *I. ricinis*; however, 10% produced 95% repellency. In a separate study, low repellency was observed against nymphal *I. ricinis* at 1% for geranium, *Pelargonium graveolens* L'Hér. ex Aiton, and lavender, *Lavandula angustifolia* Mill., oils and 100% repellency for 30% concentrations [46]. Similar results were obtained in climbing bioassays testing lavender essential oil against adult coarse-legged ticks, *Hyalomma marginatum rufipes* Koch, where the duration of repellency was dose-dependent with 20% concentrations of lavender oil providing 100% repellency for 50 min and a 5% concentration providing complete protection for only 20 min [104].

There is the popular belief that compounds of plant origin are benign and harmless to the user [27]. Increasing the concentration of plant essential oils can increase efficacy, but high concentrations may also cause contact dermatitis [92]. Additionally, many plant extracts that provide repellency against ticks exhibit toxic effects in vertebrates. For example, eugenol is an eye and skin irritant and has been shown to be mutagenic and tumerogenic [105]. β-Citronellol and 2-phenylethanol are skin irritants, and 2-phenylethanol is an eye irritant, mutagen, and tumerogen; it also affects the reproductive and central nervous systems [105]. It has been suggested that repellent compounds with toxic attributes be used as clothing treatments rather than for application directly to human skin [25].

6.3. Anti-tick pasture plants

Acaricides are the primary control method for ticks that parasitize livestock. Acaricides are problematic because they are expensive, and their use can lead to pesticide resistance, environmental pollution, and residues in meat, milk, and hides [106]. Repellent and acaricidal anti-tick pasture plants have been proposed as components of an overall integrated tick management program [107]. Essential oils and compounds (Table 3) from repellent pasture plants have been examined mostly against cattle ticks. There is one exception where Carroll et al. [44] studied a related plant species in the genus *Commiphora* against 3 ticks that bite humans. The use of anti-tick pasture plants and their actives to prevent tick feeding on humans needs further study.

Several grasses have been suggested for use in anti-tick pastures. Thompson et al. [108] conducted field trials comparing recapture rates of larval *R. microplus* released in monocultures of six pasture grass species. Molasses grass, *Melinis minutiflora* Beauv. exhibited the greatest tick deterrence with greatly reduced tick recapture rates and no re-infestation. Mwangi et al. [109] observed climbing behavior in the laboratory of *R. appendiculatus* presented simultaneously with stems of molasses grass and *Pennisetum clandestinum* Hochst. ex Chiov. (control). No *R. appendiculatus* climbed the molasses grass while 79.2–93.2% (depending on life-stage) climbed *P. clandestinum*. In field plots, no larval, 4.3% of nymphal, and 3.8% of adult *R. appendiculatus* climbed molasses grass compared to 76.2%, 65%, and 73.2% of larval, nymphal, and adults in *P. clandestinum*. Additionally, significantly fewer *R. appendiculatus* chose molasses grass leaves compared to the control in Y-olfactometer trials [109]. Repellency of Gamba grass, *Andropogon gayanus* Kunth was also tested against larval *R. microplus* [110]. Tick repellent properties were exhibited in mature grass 6–12 months old but not in plants 3 months old. The authors note that the presence of glandular trichomes on older grass and possibly a volatile compound may be responsible for the difference in repellency.

Two tropical legumes, *Stylosanthes hamata* (L.) Taub. and *S. humilis* Kunth, exhibited acaricidal and repellent properties [111]. The plants' stems and leaves are covered with glandular trichomes that produce a sticky secretion containing toxic volatiles [112]. In Y-olfactometer bioassays comparing extracts of different plant parts in various solvents, repellency ranged from 70% to 87% for *S. hamata* and 68–92% for *S. humilis* against *R. microplus* larvae [113]. Seventeen compounds were identified using GC–MS from *S. hamata* with linolenic acid being the most abundant. Sixteen compounds were identified from *S. humilis* with the compounds ferrocene and β-sitosterol being the most abundant.

A number of African plants have tick repellent properties [107]. Oil from wild basil, *Ocimum suave* Willd (an African shrub) was highly repellent against *R. appendiculatus* in climbing bioassays. No significant difference was found between deet and wild basil oil, and mortality occurred in all life stages exposed to *O. suave* oil [41]. In a climbing bioassay, essential oil from the African shrub, *Cleome monophylla* L. was as repellent as deet at a 0.1 μL dose against *R. appendiculatus* but less repellent than deet at lower doses. A number of

fractioned compounds including carvacrol, 2-dodecanone, 1-α-terpineol, and 3-undecanone from *C. monophylla* essential oil also provided equivalent repellency to deet at a dose of 0.1 μL. 2-Dodecanone and 1-α-terpineol additionally provided equivalent repellency to deet at concentrations of 0.01 and 0.001 μL, respectively [42]. Essential oil from African spiderflower, *Cleome* (*Gynandropsis*) *gynandra* (L.) Brig., was also repellent against *R. appendiculatus*. In climbing bioassays, 0.1 μL of *C. gynandra* essential oil provided 98.9% repellency compared to 84.0% repellency for an equivalent amount of deet. However, deet was more repellent than *C. gynandra* oil at 0.0001 μL, providing 70.5% versus 50.5% repellency, respectively. Fractioned compounds from *C. gynandra* (Table 3) were also highly repellent against *R. appendiculatus* providing ⩾90% repellency at 0.1 μL [43]. Malonza et al. [114] similarly found that nymphal and adult *A. variegatum* and *R. appendiculatus* avoided contact with *C. gynandra* leaves used as plugs in glass tubes. Fewer ticks were observed contacting *C. gynandra* leaves compared to tubes plugged with non-absorbent cotton wool over a 24 h period. Likewise, in olfactometer trials, significantly more nymphal and adult *R. appendiculatus* moved towards the control arm of a Y-olfactometer plugged with cotton wool than to the arm plugged with *C. gynandra* leaves. In addition to repellency by *C. gynandra*, high levels of mortality were observed in nymphal *A. variegatum* and *R. appendiculatus*. All *R. appendiculatus* nymphs died within 6–16 h, and 71% of *A. variegatum* nymphs died after 2 h of continuous exposure to the plant leaves [114].

The indigenous Maasai of Kenya and northern Tanzania use plants in the genus *Commiphora* as flea and tick repellents by employing the sap in a topical application or by consuming the boiled plant [115]. Gum haggar, *Commiphora holtziana* Engl. is an East African plant traditionally used by farmers as a tick repellent when rubbed on the skin of cattle. Birkett et al. [116] tested the resin of gum haggar against larval *R. microplus*. A hexane extract of the resin provided repellency for up to 5 h whereas a second species, *C. myrrha*, was not active. Analysis of the resins showed that *C. myrrha* contained much lower levels of sesquiterpene hydrocarbons assumed to be responsible for the repellency and that are abundant in *C. holtziana*. Kaoneka et al. [117] tested hydrodistilled oil and fractioned compounds of *C. swynnertonii* Burtt against adult *R. appendiculatus* in a climbing bioassay. Ten percent oil of *C. swynnertonii* repelled 87.3% of the ticks while deet and the fractioned compound α-copaene repelled 100%. At 1% α-copaene and deet also provided 100% repellency; however, repellency of α-copaene was significantly lower than deet at a 0.1% dose. Carroll et al. [44] tested hexane extracts of gum resin from the shrub *Commiphora erythraea* Engler against *A. americanum*, *D. variabilis*, and *I. scapularis* in climbing bioassays on treated cotton cloth. The extract provided 100% repellency against larval and adult *A. americanum* at a concentration of 0.2 mg/cm^2 and also provided significant repellency compared to controls against *D. variabilis* and *I. scapularis*. In addition, greater than 80% mortality was observed in *A. americanum* and *D. variabilis* exposed to 0.02 mg/cm^2 *C. erythraea* extract.

7. Commercially available natural repellents

Although a number of plants and plant-compounds are repellent, relatively few have been commercialized. In some cases the cost of the extraction of pure bioactive compounds is prohibitive, and the yield of these compounds may be low [27]. The active ingredients in many commercially available arthropod repellents were originally isolated from a plant or other natural source but are mass-produced synthetically. A synthetic preparation can be beneficial because of the potential of obtaining high purity and concentration of the active. A number of active ingredients commonly found in commercially available tick repellents are presented in Table 1.

7.1. IR3535

The repellent IR3535 or EBAAP (ethyl butyl acetyl aminopropionate) is a synthetic currently registered as a biopesticide by the US EPA [118] because of its structural resemblance to naturally occurring β-alanine (Table 1). IR3535 causes less irritation to mucous membranes and exhibits a safer acute oral and dermal toxicity than deet [119], and no recorded reports of adverse reactions to the product have been made [18]. IR3535 has been available in Europe since the 1970s but was not available in the US until 1999 [120]. Staub et al. [121] examined the effectiveness of a repellent containing both deet and EBAAP on human volunteers in field tests in Switzerland where the predominant tick species was *I. ricinus*. The repellent provided 41.1% repellent effectiveness and significantly fewer ticks were found attached to repellent-treated volunteers compared to those treated with a placebo. Cilek [122] determined that IR3535 was more repellent than similar concentrations of deet against nymphal *I. scapularis*. Carroll et al. [118] tested three controlled release formulations of IR3535 against nymphal *I. scapularis*. A 10% lotion formulation of IR3535 prevented ticks from crossing a treated zone on human volunteers for 9.1 h. Twenty percent aerosol and pump formulations prevented ticks from crossing the treated region for 11 and 12.2 h, respectively. However, when presented in an air stream, EBAAP was unable to inhibit attraction of *A. variegatum* to its aggregation-attraction pheromone [31], which suggests that this compound is active as a contact repellent.

7.2. PMD

The monoterpene, *para*-menthane-3,8-diol (PMD), is the major constituent of the byproduct from the distillation of leaves from the Australian lemon-scented gum tree, *Corymbia citriodora* (Hook.) K.D. Hill & L.A.S. Johnson (formerly *Eucalyptus maculata citriodon*) (Myrtaceae) (Table 1). The essential oil from *C. citriodora*, termed oil of lemon eucalyptus, contains citronella, citronellol, geraniol, isopulegol, and *delta* pinene [27]. Essential oil from *C. citriodora* was determined to provide short-term repellency against mosquitoes; however, PMD was repellent for a longer duration, likely because of its relatively low volatility [123]. In China, PMD is called Quwenling which translates to "effective repeller of mosquitoes" [27].

In addition to being repellent against several species of mosquitoes, PMD is also repellent against ticks. For example, Trigg and Hill [124] examined attachment of *I. ricinis* nymphs on the ears of rabbits treated with PMD. The proportion of nymphs that fed on rabbit ears 43 h after treatment with PMD was greatly reduced compared to untreated ears. Additionally, PMD was acaricidal with an average mortality of 77.5% on treated compared to 11.6% on untreated ears. In a field test, Gardulf et al. [125] found significantly lower tick attachment on skin treated with Citriodiol lemon eucalyptus extract compared to untreated controls. However, no significant difference was found between treated and untreated volunteers in the number of unattached crawling ticks. Jaenson et al. [46] tested oil of lemon eucalyptus and MyggA® Natural, a product similar to Citriodiol that contains 30% oil of lemon eucalyptus with a minimum of 50% PMD and small amounts of geranium, lavender, and rose extracts against nymphal *I. ricinus*. Both products provided 100% repellency 5 min after the beginning of bioassays. Field trials using cloth drags treated with MyggA® Natural or oil of lemon eucalyptus were 74% and 85% repellent, respectively, on the first day of testing. A separate field study conducted by Garboui et al. [47] showed that blankets treated with two concentrations of MyggA® Natural (3.2 and 4.2 g/m^2) and the repellent RB86 (70% neem oil containing azadirachtin) significantly reduced the number of *I. ricinus* nymphs collected by dragging compared to untreated blankets. Significantly fewer nymphs were collected on blankets trea-

ted with 4.2 g/m^2 MyggA® Natural than were collected on the other two repellent treatments.

7.3. 2-Undecanone

The repellent compound 2-undecanone (methyl nonyl ketone) was originally isolated from the glandular trichomes of the wild tomato plant, *Lycopersicon hirsutum* Dunal *f. glabratum* C.H. Müll [126] (Table 1). Resistance to insect herbivory of *L. hirsutum f. glabratum* is afforded in part by the presence of 2-undecanone. In studies against *O. parkeri*, 2-undecanone was ⩾90% repellent at 100 and 50 μg/cm^2 but was not repellent at 10 μg/cm^2 in choice-tests between treated and untreated filter paper [127].

The arthropod repellent BioUD® contains the active ingredient 2-undecanone and was registered by the US EPA in 2007. In choice-tests on treated and untreated filter paper, BioUD® with 7.75% 2-undecanone provided significantly greater mean percentage repellency than 98.1% deet against *A. americanum* and *I. scapularis* and equivalent repellency to 98.1% deet against *D. variabilis* on treated filter paper compared to untreated controls [34]. The same formulation of BioUD® was more repellent than 15% deet against *D. variabilis* in head-to-head tests directly comparing the repellents on treated filter paper. BioUD® provided high repellency against *D. variabilis* on treated cotton cheesecloth for 8 d after repellent treatments [26] and an average of 93.2% repellency against *A. americanum* over 7 weeks of testing [128]. Additionally, BioUD® was determined to be repellent against *D. variabilis* on human skin for at least 2.5 h after repellent treatment [26].

7.4. Dodecanoic acid

Dodecanoic (lauric) acid (DDA) is a saturated fatty acid that occurs as the main compound in coconut and palm kernel oil (Table 1). The tick repellent product ContraZeck® contains 10% DDA. Schwantes et al. [129] tested formulations of 10% DDA against *I. ricinus* nymphs using the moving-object bioassay [30]. Dodecanoic acid in alcohol provided a mean repellency of 86.5%. In the same study, ContraZeck® was compared to the coconut oil-based repellent Zanzarin® against *I. ricinus* nymphs and to Autan®, containing the synthetic repellent Icaridin, against *I. ricinus* adults on human skin. From 30 to 60 min after repellent application, ContraZeck® provided 83% repellency and Zanzarin® provided 94% repellency; however, repellency fell to 63% for ContraZeck® and 75% for Zanzarin® from 5.5 to 6 h. When compared to Autan®, ContraZeck® provided greater mean percentage repellency at 2, 3, and 6 h after application with repellency ranging from 75.5% to 88%.

8. Additional natural repellents

8.1. Arthropod-based repellents

Many vertebrates anoint themselves with chemicals produced by arthropods or other organisms. For example, birds and mammals have been observed to rub themselves with millipedes that excrete benzoquinones, presumably to repel ectoparasites. The potential for use of chemicals produced by arthropods as personal repellents has been known for some time and was reviewed by Jacobson in 1966 [130]. More recently, Carroll et al. [131] tested three common benzoquinone millipede defensive secretions in a climbing bioassay against nymphal *A. americanum*. One compound, 2-methoxy-3-methyl-1,4-benzoquinone, provided significant repellency compared to controls against *A. americanum* (100% at a concentration of 550 mM). After capuchin monkeys, *Cebus apella* L. in a Brazilian ecological park were observed anointing themselves with formic acid-producing ants, Falótico et al. [51] examined the repellency of formic acid and the ants themselves against nymphal Cayenne ticks, *Amblyomma cajennense* (F.) and *Amblyomma incisum* Neumann, and against adult *Amblyomma parvum* Aragão. Formic acid applied at an amount that covered human index fingers from the first to the third skin fold at a concentration of 50% repelled 100% of *A. cajennense* nymphs, 98.6% of *A. incisum* nymphs, and 86.1% of *A. parvum* adults in fingertip bioassays. Formic acid however, is highly volatile and was effective only for approximately 25 min.

8.2. Vertebrate-produced repellents

Some vertebrates produce their own chemicals that provide defense against ectoparasites [132]. The crested auklet, *Aethia cristatella* Pallas, is a seabird that produces a volatile citrus-like odorant that is secreted from wick-like feathers [133]. The odorant is predominantly comprised of even-numbered saturated and monounsaturated aldehydes [134]. These odorants appear to be important in sexual selection with auklets producing higher levels of odorant being more attractive. Prospective mating pairs of auklets rub the portions of the bodies that they are unable to self-preen (the beak, head, neck, and breast) against the wick feathers of one another [133]. A cocktail of odorant components caused a dose-dependent repellent response in *A. americanum* in a moving-object bioassay. A 10% ethanolic solution of octanal, the predominant compound in the auklet secretion, provided significantly greater repellency against nymphal *A. americanum* than blank or ethanol controls [134]. A blend of odorant components provided significant repellency compared to controls against nymphal seabird ticks, *Ixodes uriae* (White), a tick that parasitizes auklets. In the same experiment, octanal provided highly significant repellency compared to controls. Nymphal and adult *I. uriae* exposed to 5 μL of octanal became moribund within 15 min and 1 h, respectively [134].

9. Comparative activity of EPA-registered, current commercial tick repellents

Bissinger et al. [128] recently conducted comparative studies of the currently available (EPA-registered) commercial repellents for personal protection from biting arthropods, including ticks and mosquitoes. The activity of seven products containing six different active ingredients were compared in laboratory two-choice Petri dish bioassays on cotton cheesecloth against *A. americanum* and *D. variabilis* (Table 4). The products that gave the highest mean percentage repellency against both tick species were BioUD® (7.75% 2-undecanone, HOMS, LLC Clayton, NC), Cutter® (30% oil of lemon eucalyptus, Spectrum, St. Louis, MO), Jungle Juice (98.1% deet, Sawyer Products, Safety Harbor, FL), and Skin-so-soft Expedition™ Bug Guard Plus (19.6% IR3535®, Avon Products, Inc., New York, NY). There was no statistically significant difference in the mean percentage repellency provided by these four products. Slightly lower mean percentage repellency was provided by Cutter® Advanced Outdoorsman (15% Picaridin, Spectrum, St. Louis, MO) against both species. Lowest mean percentage repellency against both species was provided by the product containing 0.5% permethrin (Premium Clothing insect repellent, Sawyer Products, Safety Harbor, FL). The three most active repellents in these studies were each directly compared to BioUD® in the same Petri dish on cotton cheesecloth. BioUD® provided significantly greater overall mean percentage repellency than the IR3535® product for *A. americanum* and *D. variabilis*. BioUD® was significantly more repellent than the oil of lemon eucalyptus product for *A. americanum* but did not differ significantly in repellency against *D. variabilis*. No statistically significant difference in repellency was found between BioUD® and the deet product for either tick species [128].

Table 4
Overall mean (±1 SE) percentage repellency of seven commercially available products from 3 to 3.5 h after repellent application to cotton cheesecloth against *Amblyomma americanum* and *Dermacentor variabilis*.[a]

Active ingredient	Product	Mean (±1 SE) percentage repellency[b]	
		A. americanum	*D. variabilis*
2-Undecanone (7.75%)	BioUD® spray[d]	98.1 ± 5.2a	97.2 ± 6.1ab
DEET (98.1%)	Jungle Juice®	91.8 ± 5.2ab	100.0 ± 6.1a
IR3535 (19.6%)	Skin-So-Soft Expedition® Bug Guard Plus	92.6 ± 5.2ab	83.3 ± 6.1ab
Oil of lemon eucalyptus[c]	Cutter®[e]	88.4 ± 5.2ab	91.0 ± 6.1ab
Permethrin (0.5%)	Premium Clothing Insect Repellent[f]	68.3 ± 5.2c	97.5 ± 6.1a
Picaridin (5%)	OFF!® family care insect repellent II[g]	63.0 ± 5.2c	Not tested
Picaridin (15%)	Cutter® Advanced Outdoorsman[h]	78.2 ± 5.2bc	79.9 ± 6.1b

[a] From [128].
[b] Means in the same column followed by the same letter are not statistically significantly different ($P \leq 0.05$, pairwise comparison).
[c] 30% containing approx. 65% *para*-menthane-3,8-diol.
[d] HOMS, LLC, Clayton, NC.
[e] Sawyer Products, Safety Harbor, FL.
[f] Avon Products, Inc., New York, NY.
[g] Spectrum, St. Louis, MO.
[h] S.C. Johnson & Son, Inc., Racine, WI.

10. Importance of formulation

Repellent activity against ticks is determined by a variety of factors which include the rate of evaporation from the site of application, the importance of contact versus spatial repellency, the delivery rate to the receptor, and the potency of the compound to elicit repellent behavior. At the level of the sensilla, potency is affected by delivery of the repellent to the receptor, the affinity of the receptor protein for the repellent, degradation of the repellent in the sensilla, and potency (once in the receptor) of eliciting an effective repellent behavior. In addition, because repellents need to provide personal protection for extended periods of time, a balance must exist between all of the factors important in repellency to achieve high levels of activity for 6 h or more. A repellent might be highly volatile and therefore highly active for the first 30 min and then the active has been exhausted from the treated surface. Conditions such as abrasion, humidity, temperature, and wind also can affect the longevity of repellency [18]. Finally, because of the human factor, feel on the skin, the amount that can be applied to the skin, smell, and the perception of whether the repellent is safe affects use and ultimately whether a person will be protected from tick-borne disease. Formulation can play an important role in this equation. For example, an early field study showed that indalone formulated as an emulsion provided 83% repellency against ticks for 6 weeks compared to only 22% provided by an aerosol formulation [62]. Unfortunately, the vast majority of published research on tick repellents (discussed earlier) has focused on the discovery of active ingredients with less interest in the science of repellent formulation. Additionally, due to the proprietary nature of formulation chemistry, information on formulations is often difficult for the general research community to obtain.

Many repellents are formulated in alcohol [135]. This could pose a safety hazard to users since repellents may be applied outdoors around open flames (camping or cooking fires, gas-burning lanterns, etc.) and are flammable. In addition to posing a safety hazard, formulation in alcohol can enhance dermal absorption, as is the case with deet [135]. This absorption is partially responsible for deet's short-lived repellent action [136]. A liposomal preparation of deet (LIPODEET) was formulated in an attempt to increase the duration of its repellent protection. LIPODEET is absorbed into the skin at a 10× lower rate than deet formulated in alcohol [137]. Attachment by adult *A. americanum* and *D. variabilis* on rabbits treated with 20% formulations of deet or LIPODEET were compared. LIPODEET provided complete protection from attachment by *A. americanum* for 72 h [12]. Compared to controls, deet offered no protection from attachment by *D. variabilis* while LIPODEET-treated rabbits had 9× fewer ticks attached at 24 h and 27× fewer at 72 h. LIPODEET was also acaricidal for both *A. americanum* and *D. variabilis*. Similarly, Carroll et al. [54] showed that a polymer formulation of deet and cream formulations of SS220 and Picaridin provided approximately 100% protection against *A. americanum* nymphs for 12 h. The new polymer-coating method used to apply permethrin to cloth [73] also could be applied to other active ingredients and improved formulation technologies might be a critical factor in the improve effectiveness of a variety of repellents already described in the literature including essential plant oils.

11. Future directions

Screening of chemical libraries, the bioassay of different biological products from plants and animals, the development of structure–activity relationships, and serendipity have historically been critical factors in the research and development of repellents for personal protection from the nuisance and vector-borne pathogens associated with tick feeding. Often the first objective of these studies has been protection from mosquitoes with ticks as a secondary concern. Without question repellents need to have broad-spectrum activity to be commercially relevant and available to the public. The understanding of the mechanism of repellency from spatial versus contact to the molecular basis of odorant reception in ticks has fallen far behind that of mosquitoes. For example, over 50 different odorant-binding proteins have been identified in the mosquito, *Anopheles gambiae* Giles [33], while similar work in ticks is minimal. The recent sequencing of the *I. scapularis* genome [138] as well as new high throughput DNA sequencing technologies, the ease for the *de novo* construction of transcriptomes from sample sizes as small as a single cell, and advances in bioinformatics should lead in the near future to the rapid identification of similar proteins in ticks as well as significant advances in our overall understanding of tick repellency at the molecular level. Understanding the importance of tactile versus spatial repellency will also be critical. Although screening of chemical libraries and the examination of extracts from plants and animals will continue to be an important source for new compounds in the future, molecular and stereochemical modeling involving odorant transport, binding and degradation proteins as well as the development of *in vitro* and single cell receptor bioassays could also be important [19,33] and at the very least add to our basic knowledge of the mechanism of repellency.

A critical factor in the development of tick repellents and one that should be considered in the future even more so than in the past is the human factor. No matter how effective the repellent, public perception whether based on science or not, can affect repellent use and therefore the spread of vector-borne diseases. The growing interest in "green technologies" will likely also have an impact on repellent development and use in the future. It is the responsibility of the scientific community to understand this issue and be engaged in public education about the most effective and safe methods for personal protection. Formulation chemistry relative to tick repellents and repellents in general has been an understudied area in the scientific literature and might be a critical factor in repellent-discovery and use in the future. Finally, the development of standardized bioassays for repellency that have been validated as substitutes for tests using human volunteers and animals are needed to better evaluate the many different repellent compounds described in the literature, those to be discovered in the future and to determine relative effectiveness.

Acknowledgments

The authors thank Drs. Charles Apperson, James Harper, and Wes Watson (Dept. of Entomology, North Carolina State University, Raleigh, NC) and Dr. Christina Grozinger (Dept. of Entomology, Pennsylvania State University, University Park, PA) for comments that improved the manuscript.

References

[1] D.E. Sonenshine, R.S. Lane, W.L. Nicholson, Ticks (*Ixodida*), in: G. Mullen, L. Durden (Eds.), Medical and Veterinary Entomology, Academic Press, San Diego, 2002, pp. 517–558.
[2] D.E. Sonenshine, Biology of Ticks, vol. 2, Oxford University Press, New York, 1993.
[3] G.P. Kaaya, E.N. Mwangi, E.A. Ouna, Prospects for biological control of livestock ticks, *Rhipicephalus appendiculatus* and *Amblyomma variegatum*, using the entomogenous fungi *Beauvaria bassiana* and *Metarhizium anisopliae*, J. Invert. Pathol. 67 (1996) 15–20.
[4] Centers for Disease Control and Prevention, Rocky Mountain spotted fever. Available from: <http://www.cdc.gov/ncidod/dvrd/rmsf/prevention.htm>, 2005 (accessed 09.07.08).
[5] V.G. Dethier, L.B. Browne, C.N. Smith, The designation of chemicals in terms of the responses they elicit from insects, J. Econ. Entomol. 53 (1960) 134–136.
[6] S.P. Frances, Efficacy and safety of products containing DEET, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 337–340.
[7] H.H. Yap, K. Jahangir, J. Zairi, Field efficacy of five insect repellent products against vector mosquitoes in a tropical environment, J. Am. Mosq. Control Assoc. 16 (2000) 241–244.
[8] D.R. Barnard, R.-D. Xue, Laboratory evaluation of mosquito repellents against *Aedes albopictus*, *Culex nigripalpus*, and *Ochlerotatus triseriatus* (Diptera: Culicidae), J. Med. Entomol. 41 (2004) 726–730.
[9] C.E. Schreck, D. Fish, T.P. McGovern, Activity of repellents applied to skin for protection against *Amblyomma americanum* and *Ixodes scapularis* ticks (Acari: Ixodidae), J. Am. Mosq. Control Assoc. 11 (1995) 136–140.
[10] J.F. Carroll, J.A. Klun, M. Debboun, Repellency of deet and SS220 applied to skin involves olfactory sensing by two species of ticks, Med. Vet. Entomol. 19 (2005) 101–106.
[11] S.R. Evans, G.W. Korch Jr., M.A. Lawson, Comparative field evaluation of permethrin and DEET-treated military uniforms for personal protection against ticks (Acari), J. Med. Entomol. 27 (1990) 829–834.
[12] B. Salafsky, Y.-X. He, J. Li, T. Shibuya, K. Ramaswamy, Study on the efficacy of a new long-acting formulation of *N,N*-diethyl-*m*-toluamide (DEET) for the prevention of tick attachment, Am. J. Trop. Med. Hyg. 62 (2000) 169–172.
[13] V.B. Solberg, T.A. Klein, K.R. McPherson, J.R. Burge, R.A. Wirtz, Field evaluation of deet and a piperidine repellent (AI3-37220) against *Amblyomma americanum* (Acari: Ixodidae), J. Med. Entomol. 32 (1995) 870–875.
[14] L. Goodyer, R.H. Behrens, Short report: the safety and toxicity of insect repellents, Am. J. Trop. Med. Hyg. 59 (1998) 323–324.
[15] M. Aquino, M. Fyfe, L. MacDougall, V. Remple, West Nile virus in British Columbia, Emerg. Infect. Dis. 10 (2004) 1499–1501.
[16] United States Environmental Protection Agency, Active Ingredients found in Insect Repellents. Available from: <http://www.epa.gov/pesticides/health/mosquitoes/ai_insectrp.htm>, 2007 (accessed 16.07.08).
[17] M.S. Fradin, Mosquitoes and mosquito repellents: a clinician's guide, Ann. Intern. Med. 128 (1998) 931–940.
[18] S.J. Moore, M. Debboun, History of insect repellents, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 3–29.
[19] R.K. Gupta, A.K. Bhattacharjee, Discovery and design of new arthropod/insect repellents by computer-aided molecular modeling, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 195–228.
[20] D.H. Spach, W.C. Liles, G.L. Campbell, R.E. Quick, D.E. Anderson, T.R. Fritsche, Tick-borne diseases in the United States, N. Engl. J. Med. 329 (1993) 936–947.
[21] T.G.T. Jaenson, K. Pålsson, A.-K. Borg-Karlson, Evaluation of extracts and oils of tick-repellent plants from Sweden, Med. Vet. Entomol. 19 (2005) 345–352.
[22] H. Tunón, W. Thorsell, A. Mikiver, I. Malander, Arthropod repellency, especially tick (*Ixodes ricinus*), exerted by extract from *Artemesia abrotanum* and essential oil from flowers of *Dianthus caryophyllum*, Fitoterapia 77 (2006) 257–261.
[23] J.F. Carroll, C.L. Cantrell, J.A. Klun, M. Kramer, Repellency of two compounds isolated from *Callicarpa americana* (Lamiaceae) against *Ixodes scapularis* and *Amblyomma americanum* ticks, Exp. Appl. Acarol. 41 (2007) 215–224.
[24] S.S. Garboui, T.G.T. Jaenson, A.-K. Borg-Karlson, K. Pålsson, Repellency of methyl jasmonate to *Ixodes ricinus* nymphs (Acari: Ixodidae), Exp. Appl. Acarol. 42 (2007) 209–217.
[25] S. Del Fabbro, F. Nazzi, Repellent effect of sweet basil compounds on *Ixodes ricinus* ticks, Exp. Appl. Acarol. 45 (2008) 219–228.
[26] B.E. Witting-Bissinger, C.F. Stumpf, K.V. Donohue, C.S. Apperson, R.M. Roe, Novel arthropod repellent, BioUD, is an efficacious alternative to DEET, J. Med. Entomol. 45 (2008) 891–898.
[27] S.J. Moore, A. Lenglet, N. Hill, Plant-based insect repellents, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 275–303.
[28] E. Hess, M. Klimann, Leg sense organs in ticks, in: J.R. Sauer, J.A. Hair (Eds.), Morphology, Physiology, and Behavioral Biology of Ticks, Halstead Press, New York, 1986, pp. 361–390.
[29] D.E. Sonenshine, Biology of Ticks, vol. 1, Oxford University Press, New York, 1991.
[30] H. Dautel, O. Kahl, K. Siems, M. Oppenrieder, L. Müller-Kuhrt, M. Hilker, A novel test system for detection of tick repellents, Entomol. Exp. Appl. 91 (1999) 431–441.
[31] S. McMahon, T. Kröber, P.M. Guerin, *In vitro* assays for repellents and deterrents for ticks: differing effects of products when tested with attractant or arrestment stimuli, Med. Vet. Entomol. 17 (2003) 370–378.
[32] H. Dautel, R. Cranna, Assessment of repellency and mortality of a imidacloprid + permethrin spot-on solution against *Ixodes holocyclus* using a moving object bioassay, Aust. Vet. Practit. 36 (2006) 138–147.
[33] W. Leal, Molecular-based chemical prospecting of mosquito attractants and repellents, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 229–242.
[34] B.W. Bissinger, C.S. Apperson, D.E. Sonenshine, D.W. Watson, R.M. Roe, Efficacy of the new repellent BioUD® against three species of ixodid ticks, Exp. Appl. Acarol. 48 (2009) 239–250.
[35] S. Kumar, S. Prakash, M.P. Kaushik, K.M. Rao, Comparative activity of three repellents against the ticks *Rhipicephalus sanguineus* and *Argas persicus*, Med. Vet. Entomol. 6 (1992) 47–50.
[36] E.B. Dogan, J.W. Ayres, P.A. Rossignol, Behavioural mode of action of deet: inhibition of lactic acid attraction, Med. Vet. Entomol. 13 (1999) 97–100.
[37] M. Ditzen, M. Pellegrino, L.B. Vosshall, Insect odorant receptors are molecular targets of the insect repellent DEET, Science 319 (2008) 1838–1842.
[38] Z. Syed, W. Leal, Mosquitoes smell and avoid the insect repellent DEET, Proc. Natl. Acad. Sci. USA 105 (2008) 13598–13603.
[39] V.G. Dethier, Repellents, Annu. Rev. Entomol. 1 (1956) 181–202.
[40] H. Dautel, Test systems for tick repellents, Int. J. Med. Microbiol. 293 (2004) S182–188.
[41] E.N. Mwangi, A. Hassanali, S. Essuman, E. Myandat, L. Moreka, M. Kimondo, Repellent and acaricidal properties of *Ocimum suave* against *Rhipicephalus appendiculatus* ticks, Exp. Appl. Acarol. 19 (1995) 11–18.
[42] M. Ndungu, W. Lwande, A. Hassanali, L. Moreka, S.C. Chhabra, *Cleome monophylla* essential oil and its constituents as tick (*Rhipicephalus appendiculatus*) and maize weevil (*Sitophilus zeamais*) repellents, Entomol. Exp. Appl. 76 (1995) 217–222.
[43] W. Lwande, A.J. Ndakala, A. Hassanali, L. Moreka, N. Nyandat, M. Ndungu, H. Amiani, P.M. Gitu, M.M. Malonza, D.K. Punyua, *Gynandropsis gynandra* essential oil and its constituents as tick (*Rhipicephalus appendiculatus*) repellents, Phytochemistry 50 (1999) 401–405.
[44] J.F. Carroll, A. Maradufu, J.D. Warthen Jr., An extract of *Commiphora erythraea*: a repellent and toxicant against ticks, Entomol. Exp. Appl. 53 (1989) 111–116.
[45] P. Granett, C.F. French, Field tests of clothing treated to repel American dog ticks, J. Econ. Entomol. 43 (1950) 41–44.
[46] T.G.T. Jaenson, S. Garboui, K. Pålsson, Repellency of oils of lemon eucalyptus, geranium and lavender and the mosquito repellent MyggA Natural to *Ixodes ricinus* (Acari: Ixodidae) in the laboratory and field, J. Med. Entomol. 43 (2006) 731–736.
[47] S.S. Garboui, T.G.T. Jaenson, K. Pålsson, Repellency of MyggA Natural spray (para-menthane-3,8-diol) and RB86 (neem oil) against the tick Ixodes ricinus (Acari: Ixodidae) in the field of east-central Sweden, Appl. Exp. Acarol. 40 (2006) 271–277.
[48] M. Bar-Zeev, S. Gothilf, Field evaluation of repellents against the tick *Ornithodorus tholozani* Labou. & Mégn. in Israel, J. Med. Entomol. 11 (1974) 389–392.

[49] A. Hadani, M. Ziv, Y. Rechav, A laboratory study of tick repellents, Entomol. Exp. Appl. 22 (1977) 53–59.
[50] Z.A. Mehr, L.C. Rutledge, E.L. Morales, J.L. Inase, Laboratory evaluation of commercial and experimental repellents against *Ornithodoros parkeri* (Acari: Argasidae), J. Med. Entomol. 23 (1986) 136–140.
[51] T. Falótico, M.B. Labruna, M.P. Verderane, B.D. de Resende, P. Izar, E.B. Ottoni, Repellent efficacy of formic acid and the abdominal secretion of carpenter ants (Hymenoptera: Formicidae) against *Amblyomma* ticks (Acari: Ixodidae), J. Med. Entomol. 44 (2007) 718–721.
[52] A. Zhang, J.A. Klun, S. Wang, J. Carroll, M. Debboun, Isolongifolenone: a novel sesquiterpene repellent of ticks and mosquitoes, J. Med. Entomol. 46 (2009) 100–106.
[53] C.N. Smith, H.K. Gouck, Observations on tick repellents, J. Econ. Entomol. 39 (1946) 374–378.
[54] J.F. Carroll, J.P. Benante, J.A. Klun, C.E. White, M. Debboun, J.M. Pound, W. Dheranetra, Twelve-hour duration testing of cream formulations of three repellents against *Amblyomma americanum*, Med. Vet. Entomol. 22 (2008) 144–151.
[55] M.D. Matthewson, G. Hughes, I.S. Macpherson, C.P. Bernard, Screening techniques for the evaluation of chemicals with activity as tick repellents, Pest. Sci. 12 (1981) 455–462.
[56] E.J. Gerberg, R.J. Novak, Considerations on the use of botanically-derived repellent products, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 305–309.
[57] F.A. Morton, B.V. Travis, J.P. Linduska, Results of screening tests with materials evaluated as insecticides, miticides, and repellents at Orlando Laboratory, April, 1942 to April, 1947, US Dept. Agr. Bur. Entomol. Plant Quaran. (1947) E-733.
[58] J.M. Brennan, Preliminary report on some organic materials as tick repellents and toxic agents, Public Health Rep. 62 (1947) 1162–1165.
[59] D. Strickman, Older synthetic active ingredients and current additives, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 361–383.
[60] P. Granett, C.F. French, Further tests of dibutyl adipate as a tick repellent, J. Econ. Entomol. 44 (1951) 93–97.
[61] M.M. Cole, C.N. Smith, Tick repellent investigations at Bull's Island, S.C., 1948, J. Econ. Entomol. 42 (1949) 880–883.
[62] C.N. Smith, M.M. Cole, I.H. Gilbert, H.K. Gouck, Field tests with tick repellents – 1949, 1950, and 1952, J. Econ. Entomol. 47 (1954) 13–19.
[63] R.-D. Xue, A. Ali, J.F. Day, Commercially available insect repellents and criteria for their use, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 405–415.
[64] S.M. Kulkarni, V.M. Naik, Laboratory evaluation of six repellents against some Indian ticks, Indian J. Med. Res. 82 (1985) 14–18.
[65] M. Jensenius, A. Pretorius, F. Clarke, B. Myrvang, Repellent efficacy of four commercial DEET lotions against *Amblyomma hebraeum* (Acari: Ixodidae), the principal vector of *Rickettsia africae* in southern Africa, Trans. R. Soc. Trop. Med. Hyg. 99 (2005) 708–711.
[66] A.-M. Pretorius, M. Jensenius, F. Clarke, S.H. Ringertz, Repellent activity of DEET and KBR 3023 against *Amblyomma hebraeum* (Acari: Ixodidae), J. Med. Entomol. 40 (2003) 245–248.
[67] R.S. Lane, J.R. Anderson, Efficacy of permethrin as a repellent and toxicant for personal protection against the Pacific Coast tick and the pajaroello tick (Acari: Ixodidae and Argasidae), J. Med. Entomol. 21 (1984) 692–702.
[68] C.E. Schreck, G.A. Mount, A. Spielman, Pressurized sprays of permethrin on clothing for personal protection against the lone star tick (Acari: Ixodidae), J. Econ. Entomol. 75 (1982) 1059–1061.
[69] G.A. Mount, E.L. Snoddy, Pressurized sprays of permethrin and deet on clothing for personal protection against the lone star tick and the American dog tick (Acari: Ixodidae), J. Econ. Entomol. 76 (1983) 529–531.
[70] C.E. Schreck, E.L. Snoddy, A. Spielman, Pressurized sprays of permethrin of deet on military clothing for personal protection against *Ixodes dammini* (Acari: Ixodidae), J. Med. Entomol. 23 (1986) 396–399.
[71] M.D. Buescher, L.C. Rutledge, A. Wirtz, Studies on the comparative effectiveness of permethrin and deet against bloodsucking arthropods, Pest. Sci. 21 (1987) 165–173.
[72] R.S. Lane, Treatment of clothing with a permethrin spray for personal protection against the Western black-legged tick *Ixodes pacificus* (Acari: Ixodidae), Exp. Appl. Acarol. 6 (1989) 343–352.
[73] M. Faulde, W. Uedelhoven, Active clothing impregnation method for personal protection against ticks and biting insects, Int. J. Med. Microbiol. 296 (2006) 225–229.
[74] D.J. Fryauff, M.A. Shoukry, C.E. Schreck, Stimulation of attachment in a camel tick, *Hyalomma dromedarii* (Acari: Ixodidae): the unintended result of sublethal exposure to permethrin-impregnated fabric, J. Med. Entomol. 31 (1994) 23–29.
[75] R.M. Roe, V. Kallapur, P.A. Neese, C.S. Apperson, D.E. Sonenshine, Juvenile hormone regulation of metamorphosis and reproduction in ticks: a critical re-examination of the evidence and a new perspective, in: R.B. Halliday, D.E. Walter, H.C. Proctor, R.A. Norton, M.J. Colloff (Eds.), Acarology: Proceedings of the 10th International Congress, CSIRO Publishing, Melbourne, 2001, pp. 604–611.
[76] H. Hoogstraal, African Ixodoidea. I. Ticks of Sudan (with special reference to Equatoria Province and preliminary reviews of the genera *Boophilus*, *Margaropus*, and *Hyalomma*), US Navy Research Report NM 005 050.29.07, 1956.
[77] A. Murrell, S.C. Barker, Synonymy of *Boophilus* Curtice, 1891 with *Rhipicephalus* Koch, 1844 (Acari: Ixodidae), Syst. Parasitol. 56 (2003) 169–172.
[78] E.M. Santamaría, S.H. Fragoso, Resistencia en garrapatas *Boophilus microplus*, a los ixodicidas en Mexico, in: Proceedings, XIV Pan American Congress of Veterinary Science, 9–15 Oct. 1994, Acapulco, MX. Patrocinio Casa Autrey, S.A. de C.V., 1994, pp. 473–474.
[79] R.J. Miller, R.B. Davey, J.E. George, First report of permethrin-resistant *Boophilus microplus* (Acari: Ixodidae) collected within the United States, J. Med. Entomol. 44 (2007) 308–315.
[80] P.W. Riddles, P.A. Davey, J. Nolan, Carboxylesterases from *Boophilus microplus* hydrolyze trans-permethrin, Pest. Biochem. Physiol. 20 (1983) 133–140.
[81] J. De Jersey, J. Nolan, P.A. Davet, P.W. Riddles, Separation and characterization of the pyrethroid-hydrolyzing esterases of the cattle tick *Boophilus microplus*, Pest. Biochem. Physiol. 23 (1985) 349–357.
[82] J.H. Pruett, F.D. Guerrero, R. Hernández, Isolation and identification of an esterase from a Mexican strain of *Boophilus microplus* (Acari: Ixodidae), J. Econ. Entomol. 95 (2002) 1003–1007.
[83] A. Heller-Haupt, M.G.R. Varma, The effect of age on susceptibility of two species of African ticks (Ixodidae) to synthetic pyrethroids, Trop. Pest. Manag. 28 (1982) 385–392.
[84] S.S. Rao, U. Kaveeshwar, S.S. Purkayastha, Acute oral toxicity of insect repellent *N,N*-diethylphenylacetamide in mice, rats, and rabbits and protective effect of sodium pentobarbital, Indian J. Exp. Biol. 31 (1993) 755–760.
[85] S.S. Rao, M.S. Agarwal, K.M. Rao, R.V. Swamy, Study on dermal toxicity and urinary metabolites of the new insect repellent *N,N*-diethylphenylacetamide in rabbits, Toxicol. Lett. 45 (1989) 67–72.
[86] S.S. Rao, R.V. Swamy, P.K. Ramachandran, Toxicity and metabolism of a new insect repellent *N,N*-diethylphenylacetamide in mice, rats, and guinea pigs on cutaneous application, Toxicology 58 (1989) 81–89.
[87] T.P. McGovern, C.E. Schreck, J. Jackson, Mosquito repellents: alicyclic amides as repellents for *Aedes aegypti* and *Anopheles quadrimaculatus*, Mosq. News 38 (1978) 346–349.
[88] J.F. Carroll, V.B. Solberg, J.A. Klun, M. Kramer, M. Debboun, Comparative activity of deet and AI3-37220 repellents against the ticks Ixodes scapularis and Amblyomma americanum (Acari: Ixodidae) in laboratory bioassays, J. Med. Entomol. 41 (2004) 249–254.
[89] J.A. Klun, W.F. Schmidt, M. Debboun, Stereochemical effects in an insect repellent, J. Med. Entomol. 38 (2001) 809–812.
[90] United States Environmental Protection Agency, New pesticide fact sheet: Picaridin. Available from: <http://www.epa.gov/opprd001/factsheets/picaridin.pdf>, 2005 (accessed 23.06.09).
[91] S.P. Frances, Picaridin, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 311–326.
[92] D.R. Barnard, Repellency of essential oils to mosquitoes (Diptera: Culicidae), J. Med. Entomol. 36 (1999) 625–629.
[93] United States Environmental Protection Agency, What are biopesticides? Available from: <http://www.epa.gov/pesticides/biopesticides/whatarebiopesticides.htm>, 2008 (accessed 01.12.08).
[94] D.A. Levin, The chemical defenses of plants to pathogens and herbivores, Annu. Rev. Ecol. Syst. 7 (1976) 121–159.
[95] J.H. Langenheim, Higher plant terpenoids: a phytocentric overview of their ecological roles, J. Chem. Ecol. 20 (1994) 1223–1280.
[96] L.F. Kappers, M. Dicke, H.J. Bouwmeester, Terpenoids in plant signaling, chemical ecology, in: T.P. Begley (Ed.), Wiley Encyclopedia of Chemical Biology, John Wiley & Sons, Inc., Hoboken, NJ, 2008, pp. 1–8.
[97] W. Thorsell, A. Mikiver, H. Tunón, Repelling properties of some plant materials on the tick *Ixodes ricinus* L, Phytomedicine 13 (2006) 132–134.
[98] K. Pållson, T.G.T. Jaenson, P. Bæckström, A.-K. Borg-Karlson, Tick repellent substances in the essential oil of *Tanacetum vulgare*, J. Med. Entomol. 45 (2008) 88–93.
[99] N.A. Panella, J. Karchesy, G.O. Maupin, J.C.S. Malan, J. Piesman, Susceptibility of immature *Ixodes scapularis* (Acari: Ixodidae) to plant-derived acaricides, J. Med. Entomol. 34 (1997) 340–345.
[100] N.A. Panella, M.C. Dolan, J.J. Karchesy, Y. Xiong, J. Peralta-Cruz, M. Khasawneh, J.A. Montenieri, G.O. Maupin, Use of novel compounds for pest control: insecticidal and acaricidal activity of essential oil components from heartwood of Alaska yellow cedar, J. Med. Entomol. 42 (2005) 352–358.
[101] G. Dietrich, M.C. Dolan, J. Peralta-Cruz, J. Schmidt, J. Piesman, R.J. Eisen, J. Karchesy, Repellent activity of fractioned compounds from *Chamaecyparis nootkatensis* essential oil against nymphal *Ixodes scapularis* (Acari: Ixodidae), J. Med. Entomol. 43 (2006) 957–961.
[102] R.A. Creelman, J.E. Mullet, Biosynthesis and action of jasmonates in plants, Annu. Rev. Plant Physiol. Plant Mol. Biol. 48 (1997) 355–381.
[103] M.S. Fradin, J.F. Day, Comparative efficacy of insect repellents against mosquito bites, N. Engl. J. Med. 347 (2002) 13–18.
[104] M.N. Mkolo, M.R. Magano, Repellent effects of the essential oil of *Lavendula angustifolia* against adults of *Hyalomma marginatum rufipes*, J. S. Afr. Vet. Assoc. 78 (2007) 149–152.
[105] R.J. Lewis, Sax's Dangerous Properties of Industrial Materials, ninth ed., Van Nostrand Reinhold, New York, 1996.

[106] J.J. de Castro, Sustainable tick and tickborne disease control in livestock improvement in developing countries, Vet. Parasitol. 71 (1997) 77–97.
[107] G.P. Kaaya, The potential for anti-tick plants as a component of an integrated tick control strategy, Ann. NY Acad. Sci. 916 (2000) 576–582.
[108] K.C. Thompson, J. Rao, T. Romero, Antitick grasses as the basis for developing practical tropical tick control packages, Trop. Anim. Health Prod. 10 (1978) 179–182.
[109] E.N. Mwangi, S. Essuman, G.P. Kaaya, E. Nyandat, D. Munyinyi, M. Kimondo, Repellence of the tick *Rhipicephalus appendiculatus* by the grass *Melinis minutiflora*, Trop. Anim. Health Prod. 27 (1995) 211–216.
[110] C. Cruz-Vazquez, M. Fernández-Ruvalcaba, Anti-tick repellent effect of *Andropogon gayanus* grass on plots of different ages experimentally infested with *Boophilus microplus* larvae, Parasitol. al Día 24 (2000) 88–91.
[111] M. Fernandez-Ruvalcaba, C. Cruz-Vazquez, G. Solano-Vergara, Z. Garcia-Vazquez, Anti-tick effects of *Stylosanthes humilis* and *Stylosanthes hamata* on plots experimentally infested with *Boophilus microplus* larvae in Morelos, Mexico, Exp. Appl. Acarol. 23 (1999) 171–175.
[112] R.W. Sutherst, R.J. Jones, H.J. Schnitzerling, Tropical legumes of the genus *Stylosanthes* immobilize and kill cattle ticks, Nature 295 (1982) 320–321.
[113] F. Muro Castrjón, C. Cruz-Vázquez, M. Fernández-Ruvalcaba, J. Molina-Torres, J. Soria Cruz, M. Ramos Parra, Repellence of *Boophilus microplus* larvae in *Stylosanthes humilis* and *Stylosanthes hamata* plants, Parasitol. Latinoam. 58 (2003) 118–121.
[114] M.M. Malonza, O.O. Dipeolu, A.O. Amoo, S.M. Hassan, Laboratory and field observations on anti-tick properties of the plant *Gynandropsis gynandra* (L.) Brig, Vet. Parasitol. 42 (1992) 123–136.
[115] N. Kilongozi, Z. Kengera, S. Leshongo, The utilization of indigenous knowledge in range management and forage plants for improving livestock productivity and food security in the Masai and Barbaig communities of Kibaha. Food and Agriculture Organization of the United Nations LinKS project – Report 41, 2005.
[116] M.A. Birkett, S. Al Abassi, T. Kröber, K. Chamberlain, A.M. Hooper, P.M. Guerin, J.A. Pettersson, R. Slade, L.J. Wadhams, Antiectoparasitic activity of the gum resin, gum haggar, from the East African plant, *Commiphora holtziana*, Phytochemistry 69 (2008) 1710–1715.
[117] B. Kaaneka, M. Mollel, F. Lyatuu, Leaf essential oil composition and tick repellency activity of *Commiphora swynnertonii* Burtt, J. Biol. Res. Thessaloniki 8 (2007) 213–216.
[118] S.P. Carroll, Prolonged efficacy of IR3535 repellents against mosquitoes and blacklegged ticks in North America, J. Med. Entomol. 45 (2008) 706–714.
[119] G. Nentwig, Use of repellents as prophylactic agents, Parasitol. Res. 90 (2003) S40–S48.
[120] G. Puccetti, IR3535 (ethyl butylacetylaminoproprionate), in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 353–360.
[121] D. Staub, M. Debrunner, L. Amsler, R. Steffen, Effectiveness of a repellent containing DEET and EBAAP for preventing tick bites, Wilderness Environ. Med. 13 (2002) 12–20.
[122] J.E. Cilek, Repellent efficacy of IR3535 and DEET against nymphal blacklegged ticks (*Ixodes scapularis*). in: Proc. IXth International Conference on Lyme *Borreliosis* and other Tick-borne Diseases, New York, NY, 2002, pp. 18–22.
[123] S.S. Barasa, I.O. Ndiege, W. Lwande, A. Hassanali, Repellent activities of stereoisomers of p-menthane-3,8-diols against Anopheles gambiae (Diptera: Culicidae), J. Med. Entomol. 39 (2002) 736–741.
[124] J.K. Trigg, N. Hill, Laboratory evaluation of a eucalyptus-based repellent against four biting arthropods, Phytother. Res. 10 (1996) 313–316.
[125] A. Gardulf, I. Wohlfart, R. Gustafson, A prospective cross-over field trial shows protection of lemon eucalyptus extract against tick bites, J. Med. Entomol. 41 (2004) 1064–1067.
[126] R.R. Farrar, G.G. Kennedy, 2-Undecanone, a constituent of the glandular trichomes of *Lycopersicon hirsutum f. glabratum*: effects on *Heliothis zea* and *Manduca sexta* growth and survival, Entomol. Exp. Appl. 43 (1987) 17–23.
[127] M.B. Vanderherchen, Trypsin Modulating Oostatic Factor (TMOF) and Non-peptidic Analogs as Novel Insecticides and Arthropod Repellents, M.S. Thesis, North Carolina State University, Raleigh, NC USA, 2003, 76 pp.
[128] B.W. Bissinger, J. Zhu, C.S. Apperson, D.E. Sonenshine, D.W. Watson, R.M. Roe, Comparative efficacy of BioUD6 to other commercially available arthropod repellents against the ticks, *Amblyomma americanum* and *Dermacentor variabilis* on cotton cloth, Am. J. Trop. Med. Hyg., in press. Q1
[129] U. Schwantes, H. Dautel, G. Jung, Prevention of infectious tick-borne diseases in humans: comparative studies of the repellency of different dodecanoic acid-formulations against *Ixodes ricinus* ticks (Acari: Ixodidae), Parasitol. Vectors 1 (2008) 8–19.
[130] M. Jacobson, Chemical insect attractants and repellents, Annu. Rev. Entomol. 11 (1966) 403–422.
[131] J.F. Carroll, M. Kramer, P.J. Weldon, R.G. Robbins, Anointing chemicals and ectoparasites: effects of benzoquinones from millipedes on the lone star tick *Amblyomma americanum*, J. Chem. Ecol. 31 (2005) 63–75.
[132] P.J. Weldon, J.F. Carroll, Vertebrate chemical defenses: secreted and topically acquired deterrents of arthropods, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 47–75.
[133] H.D. Douglas III, Prenuptial perfume: alloanointing in the social rituals of the crested auklet (*Aethia cristatella*) and the transfer of arthropod deterrents, Naturwissenschaften 95 (2008) 45–53.
[134] H.D. Douglas III, J.E. Co, T.H. Jones, W.E. Conner, Interspecific differences in *Aethia spp.* auklet odorants and evidence for chemical defense against ectoparasites, J. Chem. Ecol. 30 (2004) 1921–1935.
[135] I. Stinecipher, J. Shah, Percutaneous permeation of *N,N*-diethyl-*m*-toluamide (DEET) from commercial mosquito repellents and the effect of solvent, J. Toxicol. Environ. Health 52 (1997) 119–135.
[136] B. Salafsky, K. Ramaswamy, Y.-X. He, J. Li, T. Shibuya, Development and evaluation of LIPODEET, a new long-acting formulation of *N,N*-diethyl-*m*-toluamide (DEET) for the prevention of schistosomiasis, Am. J. Trop. Med. Hyg. 61 (1999) 743–750.
[137] B. Salafsky, T. Shibuya, Y.-X. He, J. Ha, K. Ramaswamy, Lipodeet: an improved formulation for a safe long-lasting repellent, in: M. Debboun, S. Frances, D. Strickman (Eds.), Insect Repellents: Principles, Methods, and Uses, CRC Press, Boca Raton, 2007, pp. 311–326.
[138] VectorBase, *Ixodes scapularis*. Available from: <http://iscapularis.vectorbase.org/index.php>, 2009 (accessed 19.02.09).
[139] SciFinder Scholar, American Chemical Society, 2006.